Title: Cost-effectiveness of a pragmatic exercise intervention for women with breast cancer: results from a randomized, controlled trial.

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Abstract

Objective: To report on the cost-effectiveness of the Exercise for Health trial, comparing an exercise intervention with usual care during and following treatment for women with breast cancer.

Methods: Women with breast cancer were randomized to an eight-month exercise intervention (involving regular contact with an exercise physiologist over the phone, n=67, or home-delivered face-to-face, n=67) or usual care (n=60) group and were assessed pre-intervention (five weeks post-surgery), mid-intervention (six months post-surgery) and 10 weeks post-intervention (12 months post-surgery). The benefit measures were 'number of improvers' in quality of life (QoL; FACT-B+4) and quality-adjusted life years (QALYs; EQ-5D-3L). Data on provider, patient and government costs were used to consider two cost scenarios: 1) a service provider model and, 2) a private model.

Results: There were 69 improvers in the intervention group compared with 21 in the usual care group (odds ratio 2.09, 95% CI: 1.08, 4.01, p=0.033). The incremental cost per improver was AU\$2,282-\$2,644. QALY gain for the intervention group versus the usual care group was 0.009, with incremental cost per QALY gain for model one and two being AU\$105,231 and AU\$90,842, respectively. However, sensitivity analyses indicate that incremental cost per QALY gained was volatile to EQ-5D-3L weights.

Conclusions: Findings suggest that a pragmatic exercise intervention yields more women with markedly improved QoL after breast cancer than usual care and may be cost-effective. The results are less certain in terms of incremental cost per QALYs, however this may be an inappropriate measure for reflecting exercise benefit for women with breast cancer.

Keywords: cost-effectiveness, exercise intervention, breast cancer, oncology, quality-adjusted life years

Background

Long-term sequelae of breast cancer treatment are common; 60-70% of breast cancer survivors live with chronic adverse treatment-related side effects, such as upper-body symptoms, lymphoedema and/or fatigue [1]. Younger women can experience premature menopause, bone density loss, infertility and associated distress [2]. With increasing numbers of women diagnosed with breast cancer each year, together with improving survival rates, the need to understand treatment-related concerns and to identify safe, effective, evidence-based strategies to alleviate these side effects and improve quality of life is important.

International cancer organisations recommend cancer survivors to engage in regular physical activity, eat a healthy diet and aim to keep their weight within a healthy range [3, 4]. Regular, moderate-intensity exercise confers numerous quality of life benefits to women during and following breast cancer treatment [5-10]. Exercise may prevent common and debilitating treatment-related side effects (i.e., fatigue, lymphoedema and weight gain)[5, 11-14] and can improve compliance to adjuvant treatment [15]. Further, evidence from a meta-analysis using data from high quality breast cancer cohort studies, as well as evidence from a recent randomized trial evaluating exercise during chemotherapy for breast cancer, demonstrate a relationship between exercise after diagnosis and improved overall and breast cancer-specific survival, and reduced risk of breast cancer recurrence [16-18]. Thus, the potential impact to individuals through the integration of exercise within standard breast cancer therapy is significant. Unfortunately, most women with breast cancer are insufficiently active (based on national, physical activity guidelines),[19-21] and exercise is not routinely prescribed as part of their care.

We completed a pragmatic, randomized, controlled trial designed to evaluate the feasibility and effectiveness of an eight-month exercise intervention for women commencing six weeks post-surgery for breast cancer [22]. The trial, Exercise for Health (EfH), was delivered one-on-one by a trained exercise physiologist either home-delivered face-to-face or over the telephone. The intervention, irrespective of mode of delivery, was found to be both feasible and effective in preventing declines in fitness and function and improving quality of life during treatment and in facilitating recovery post-treatment [23]. The face-to-face delivery mode reflects the traditional approach used by exercise physiologists in the prescription of exercise and, at least in some countries such as Australia, there already exists public and private health reimbursement for use of such allied health services via

this mode. The telephone-delivery mode reflects a modality with broad population reach and with the potential for scalability in partnership with cancer organisations offering support and information via telephonic services [24].

Expenditure on healthcare resources is increasingly scarce and therefore new interventions need to demonstrate acceptable patient benefits to justify the additional investment. Cost-effectiveness analysis is a useful method in which to weigh the costs and consequences of interventions against other options. Consequently, the purpose of this study was to report on the cost-effectiveness comparing the EfH exercise intervention with usual care for women with breast cancer through either face-to-face or telephone delivery modes.

Methods

The EfH trial (ACT RN: 012606000233527) was approved by the Human Research Ethics Committee at the Queensland University of Technology and at each of the four participating hospitals. Investigators obtained informed consent from each participant.

Sample and Intervention Description

The EfH intervention was a prospective, three-arm randomized controlled trial evaluating an eight-month exercise program for women after surgery for primary breast cancer. The study participants (n=194) were women who were newly diagnosed with breast cancer, and were recruited from four participating hospitals in Brisbane (Australia) between October 2006 and June 2008. Women were eligible for the study if they were aged between 20-69 years and resided within 30 kilometres (18.6 miles) of Brisbane central business district. The intervention was delivered through either face-to-face home delivery or by telephone over an eight-month period starting six weeks after breast surgery. The intervention involved 16 scheduled sessions by a trained and qualified exercise physiologist. The sessions were weekly to begin with and became less frequent (monthly) towards the end of the intervention period to promote ongoing patient-driven exercise beyond the study end. The overall goal was for women to be exercising at least four days per week for 45 minutes, including aerobic and resistance-based exercise. The usual care group received no regular or formal advice outside of their routine healthcare contacts during the post-surgical period of the study. Women were randomized into one of the three groups via a computer-generated unblocked sequence of random numbers. Full details of the trial methods, sample and intervention outcomes have been previously published [22, 23].

Data Collection

Data were collected at baseline (six weeks post-surgery), mid-intervention (six months post-surgery) and post-intervention (12 months post-surgery). At baseline, data items included standard socio-demographics, cancer disease and treatments, and a range of physical tests performed by centrally-trained-to-study-protocol exercise physiologists blinded to group allocation. For the current analysis, the main outcomes were: number of women with improved quality of life; quality-adjusted life years (QALYs); and intervention costs.

Previously, the EfH intervention has demonstrated significant patient benefits for quality of life, fitness and fatigue [23]. For the present analysis, the number of women who reported substantial improvements in quality of life was used as a clear indicator of benefit. The FACT-B+4 questionnaire is a multi-dimensional tool, designed to assess quality of life for women with breast cancer. Quality of life ‘improvers’ were those who reported a clinically important increase of ≥ 8 points [25] on the FACT-B+4 score (score range: 0-160) between baseline to 12 months post-surgery. As a secondary outcome, due to being generic and widely used in economic evaluations, QALYs were also considered. QALYs are a generic outcome which combine life years (or survival) and quality of life or health utility. We used the Australian algorithm [26] to obtain a EuroQol-5D (EQ-5D-3L) weight (range zero to one) and derived QALYs for each participant. In women with breast cancer, convergent validity, internal consistency and test-retest reliability for the EQ-5D-3L is $r > 0.49$, $\alpha = 0.71$ and $\kappa = 0.7$, respectively [27].

The types of costs included in the analysis were taken from a broad perspective covering health providers, patients and government. Two cost scenarios were considered: 1) a service provider model, where the intervention could be implemented by a community organisation supporting people with cancer and where the exercise physiologist is an employee of the organisation and, 2) a private model, where exercise physiologists working privately could integrate the intervention into their routine practice. In the first scenario the costs of labour, intervention materials and resources are included as costs to the community organisation however in the second scenario the government payments to the private exercise physiologist includes the labour and all other provisions. Furthermore, the private exercise physiologist would already have these items for all other types of patients and by costing additional intervention resources and materials, this was considered double-counting. In the service provider model, costs were incurred by the provider and patients. Project records provided the

quantities and most monetary values for intervention resources in the service provider model. These included: exercise physiologist and administrative salaries, participant education booklets and supportive materials, a range of exercise measurement devices and hand weights, telephone expenses, office consumables and rental and marketing expenses. Patient out-of-pocket expenses were included for exercise-related costs and fees for the private exercise physiologist. In the private model, the costs were incurred by the Australian Government that subsidises services by private, accredited exercise physiologists through the Medicare Benefits Schedule [28]. The private model also included patient out-of-pocket expenses but excluded patient travel costs (due to the home-delivered intervention). In both scenarios, costs relating to the routine healthcare for breast cancer were omitted because these were not expected to differ across the intervention and control arms. No exercise injuries occurred in the trial. Although the face-to-face and telephone intervention modes were separated in the main trial, here they were pooled because intervention resources were virtually identical, with the exception of vehicle leasing in the service provider model. Vehicle leasing was estimated at current commercial rates which included financing, fuel and all servicing for a small car. Costs for the usual care group were minimal and included patient out-of-pocket expenses collected in the trial.

Data Analyses

An intention-to-treat approach was taken to assess differences in the outcomes across the trial arms. All baseline socio-demographic and medical characteristics were compared across the intervention and control arms using Chi-square tests for categorical data and Student's t-tests for continuous data. Comparing across treatment arms, the minimal important difference for the EQ-5D-3L is in the range of 0.06-0.09 points [27]. Generalised estimating equations models were used to assess both time and treatment main and interaction effects. QALYs were calculated using all assessments of EQ-5D-3L and the area-under-the-curve method to produce a single QALY for each person over 12 months [29]. Intervention costs were tallied for all components of the respective cost scenarios. An equivalent annual cost was used for exercise equipment [29]. The key outcomes were combined into ratios of incremental cost per improver and incremental cost per QALY. These provide the *relative* cost and health benefits of the intervention versus usual care. Costs were presented in 2014 Australian dollars.

One-way sensitivity analyses were undertaken for the calculated QALYs using the 95% confidence interval for each group and variation in car leasing costs, representing plausible low and high QALYs and cost scenarios.

Patient costs for exercise equipment in the intervention group were self-reported but were unknown for the usual care group. In the base case, it was assumed 50% of the intervention group costs would apply to the usual care group and this was tested at 25%, 75% and 100% in sensitivity analyses. As most costs in the service provider model were collected and valued with point estimates, we also assessed group costs at $\pm 30\%$ in a sensitivity analysis. Finally, a probabilistic sensitivity analysis was undertaken to assess the likelihood of the intervention being cost-effective. Here simulation methods were applied and variables for cost and QALYs were varied simultaneously. Variations in estimates were made using beta distributions for QALYs (using statistical means and standard deviations) and normal distributions for costs (based on means and estimated standard deviations: $sd = \text{mean}/6$). This analysis was performed in TreeAge Pro 2014 [30]. To interpret the results, a ratio of AU\$50,000 per QALY gain was used as an acceptable threshold for cost-effective health care in line with reimbursement decisions in Australia [31].

Results

The intervention and usual care groups were similar with respect to their socio-demographic and clinical characteristics. Women had an average age of 52 ± 8 years, were overweight (mean body mass index = 26.6 ± 5.2 kg/m²), and 30% and 62% were classified as having stage I and II+ disease, respectively [22].

The number of improvers was 69 (57%) in the intervention group versus 21 (39%) in the usual care group; an intervention effect of 48 additional women exceeding clinically meaningful changes in their health-related quality of life (odds ratio 2.09, 95% CI: 1.08, 4.01, $p = 0.033$). Table 1 presents the utility scores at baseline, and at 6- and 12-months post-surgery, as well as changes in scores over time. The interaction effect between time and group was statistically significant ($p < 0.05$). Compared with the usual care group, the intervention group reported minimally relevant improvements in EQ-5D-3L weights from baseline to 12 months post-treatment ($p < 0.05$). In contrast, weights for the usual care group remained relatively stable over time (Table 1). The mean costs per patient for the intervention through a service provider model were \$967, \$838 for the private model and \$20 for usual care (Table 2). The highest proportion of total costs in the service provider model was labour costs (78%) and vehicle leasing costs (5%).

Compared with usual care, the intervention required an additional \$947 to \$818 (depending on service model) to produce 48 additional women with significant improvements to their quality of life or an incremental cost of

\$2,282 to \$2,644 per improver (Table 3). Using the secondary outcome of QALYs, the incremental QALY gain for the intervention group was minor at 0.009 (Table 3). Compared with usual care, the cost per QALY gain was \$90,842 and \$105,231 for the two service models (Table 3). In the sensitivity analyses, variation in costs changed the cost per improver between \$1,756 and \$3,777 (Table 4). If the intervention reduced the number of additional ‘improvers’ by 30% from 48 to 34, the incremental cost would be \$3,261 to \$3,777 per improver. Sensitivity analyses indicated that the incremental cost effectiveness ratios using QALYs gained were most sensitive when the EQ-5D-3L weights were varied within the 95% confidence limits. The results ranged from \$16,685 per QALY gain to usual care being superior (i.e., less expensive and higher QALYs) (Table 4). Other variations in variables tested (e.g., leasing costs) produced negligible changes to the incremental cost effectiveness ratios. The likelihood of the service provider model being cost-effective was 44.4%, and 46.3% for the private model, at a willingness-to-pay threshold of AU\$50,000 per QALY gain [31].

Discussion

In terms of the numbers of women reporting clinically significant improvements in quality of life, the intervention, using either service model, may be cost-effective at approximately AU\$2,400 per improver (or AU\$300 per month). Notably, the total and mean intervention costs for either service model were low for an 8-month intervention and up to 16 contact sessions per patient. However, the cost effectiveness of the intervention, for either service model, was more uncertain using QALYs gained as a secondary outcome. These latter findings showed high volatility to the EQ-5D-3L weights and the likelihood of being cost-effective was 44-46%. In this study, the EQ-5D-3L was not sensitive to capture the intervention effect and therefore QALYs were not entirely appropriate for this context. While QALYs are the preferred outcome in health economic evaluations, a number of reasons reduce their usefulness here. The intervention duration was not expected to extend participant survival during the trial period. The mean health utility weight for our participants (0.84) was similar to those reported for the Australian general population (0.83 [32] and 0.89 [26]). Therefore, detecting differences in QALYs was unrealistic in our sample.

The EfH intervention was designed to provide women with the skills and confidence to continue their physical activity regimens beyond the trial. Although we do not demonstrate the ongoing sustainability of these potential benefits, at a cost of approximately AU\$2,400 per improver, the intervention produced several health benefits to participants at costs significantly less than for surgical or radiotherapy services. With growing numbers of

women surviving breast cancer treatment, funding for programs and services in the survivorship phase of cancer care is equally important as services in the diagnostic and treatment phases, if benefits are potentially life-long. Further, it seems likely that cost-effectiveness of exercise programs would be influenced and improved by high throughput, which will be dependent on institutional commitment and clinician support.

When health-related quality of life data were reviewed further, ceiling effects pre-intervention were observed for 25% of the intervention group and 33% of the usual care group. Also of note is that the EfH sample was likely more active at baseline compared with the wider breast cancer population [22]. This is not unique to the EfH trial and has been previously identified as a limitation of the generalizability of findings from the majority of exercise intervention trials involving women with breast cancer [33]. Both factors (that is, high quality of life scores and being physically active at time of study commencement) may mean that the intervention and usual care group health utility weights were more similar than might otherwise be true. This would underestimate health utility weights in our cost-effectiveness findings and result in a higher incremental cost per QALY ratio. In addition, several important intervention benefits found in the intervention group, including improved fatigue and fitness,[23] may not be adequately incorporated within these cost-effectiveness analyses. For example, while the FACT-B+4 includes an item for fatigue, it is not a validated fatigue tool; fitness benefits observed were objectively measured.

Three studies have reported on the cost-effectiveness of exercise interventions among women diagnosed with breast cancer,[34-36] and one for patients with lung cancer [37]. Similarly to our study, the previous cost-effectiveness studies used both short-term patient outcomes and supplemented these with QALYs. Two of the breast cancer studies were based on randomized, controlled trials but the time horizons (12 months to five years), the types of interventions (one multimedia, on prescribed 12-week physical exercise), frequency of contacts with allied health professionals (no regular contact, once only) and the characteristics of the samples and costing components varied substantially. Unsurprisingly, there were mixed results with the 12-week physical exercise intervention found to be cost-effective, while the multimodal intervention was not. Further, neither trial assessed the cost-effectiveness of an exercise intervention that is designed and implemented according to exercise guidelines endorsed by a major cancer organisation (including the American Cancer Society) or exercise science body, such as the American College of Sports Medicine.

Conclusion

In summary, an exercise intervention for women after diagnosis of breast cancer may be cost-effective if society is willing to pay ~AU\$300 per month for women with breast cancer to have markedly improved quality of life. As such, findings from this study, which evaluated an exercise intervention in the real-world setting may also be affordable and beneficial from a public health perspective. Exercise is fast becoming considered an evidence-based adjuvant treatment for cancer and these findings highlight its potential affordability.

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Conflict of Interest: The authors declare they have no conflicts of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1: Health utility weights^a at pre-intervention, mid-intervention and post-intervention

	Pre-intervention		Mid-intervention (6 months post-surgery)		Post-intervention (12 months post-surgery)		p-value time x group interaction	Δ mid-pre scores ^b	Δ post-pre scores ^b
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)		Δ (95% CI)	Δ (95% CI)
EQ-5D-3L							0.037		
Intervention	0.79	(0.77, 0.82)	0.83	(0.80, 0.86)	0.86	(0.84, 0.89)		0.04 (0.01, 0.06)	0.07 ^{c, d} (0.04, 0.10)
Usual care	0.83	(0.80, 0.87)	0.81	(0.76, 0.87)	0.85	(0.81, 0.89)		-0.02 (-0.07, 0.03)	0.02 (-0.03, 0.06)

^a EQ-5D-3L: EuroQol5D utility score with Australian weights applied (range 0 = worse health state to 1 = best health state); change over time or difference between groups of ≥ 0.06 units is clinically important (Source: Pickard et al., 2007).

^b Δ mid-pre scores = change between baseline to six months post-surgery utility scores; Δ post-pre scores = change between baseline to 12 months post-surgery utility scores

^c Clinically meaningful difference between groups compared to the usual-care group.

^d Clinically meaningful change over time.

Table 2: Intervention resources and costs by intervention provider type (AU\$ 2014)

	Service provider model			Private model		
	n	Mean cost \$	Total \$	n	Unit cost \$	Total \$
Patient costs						
Exercise clothing, equipment & other	134	40.46	5,422.00	134	40.46	5,422.00
Fees for accredited exercise physiologist	0	0	0	134	9.30	1,246.20
Sub-total		40.46	5,422.00		49.76	6,668.20
Government costs ¹						
GP chronic disease management services, prerequisite ²	0	0	0	134	258.55	34,645.70
Exercise physiologist MBS fee – 10 visits ³	0	0	0	134	529.50	70,953.00
Sub-total		0	0		788.05	105,598.70
Personnel						
Exercise physiologists, 16 hours/participant	134	758.53	101,643.34			
Administrative staff, 3.5 hours/week for 16 weeks = 56 hours total	134	17.13	2,296.00			
Sub-total		775.67	103,939.34		0	0
Intervention Materials						
Educational workbook exercise tracker						
Case management folder, 1 per participant	134	9.40	1,259.60			
Sub-total		9.40	1,259.60		0	0
Resources and other	Number purchased					
Junsd Stopwatch	4	13.57	54.29			
First Aid Kit	4	96.87	387.48			
Resuscitation masks	4	25.07	100.27			
Spyhgo, classroom set	4	66.24	264.94			
Goniometer, Robinson Pocket	4	48.50	193.99			
Dynamometer, Advanced Hand	4	290.99	1,163.96			
Scale, Platform Medical	4	332.56	1,330.24			
Polar FS1	4	102.54	410.16			
Dumbbell hand weights x 5 sets	5	230.00	1,150.00			
	n		5,055.35			
Sub-total Annual equivalent cost	134	13.85	1,856.37		0	0
Intervention delivery						
Marketing costs	134	37.31	5,000.00			
Office rental	134	38.80	5,199.00			
Phone charges - assumed mobile plan \$110 per month x 8 months	134	6.57	880.00			
1 car lease for 8 months \$349.90 / fortnight for 17.33 fortnights	134	45.25	6,063.77			
Sub-total		127.93	17,142.77		0	0
TOTAL AU Dollars 2014		\$967.31	\$126,620		\$837.81	\$112,267

1. Under the service provider arrangement the exercise physiologist would not be additionally charging patients for services and there would not be costs incurred by government.

2. Prerequisite items of 721 and 723 for GP services are necessary for referral to the exercise physiologist.

3. Exercise physiologist under the chronic disease management MBS item 10953, maximum five sessions allowed each calendar year. Here 10 sessions assumed to cross two calendar years.

Table 3: Costs, Improvers, QALYs and incremental cost-effectiveness ratios (AU\$ 2014)

	Costs		Improvers ¹		QALYs		ICER ²	ICER ³
	Mean	Incr	#	Incr	Mean	Incr	Improvers	QALYs
Intervention - Service	\$967	\$947	69	48	0.846	0.009	\$2,644	\$105,231
Intervention - Private EP	\$838	\$818					\$2,282	\$90,842
Usual care	\$20	ref	21	ref	0.837	ref	ref	ref

EP = exercise physiologist ICER = incremental cost-effectiveness ratio, Incr – incremental, QALYs = quality-adjusted life years

1. Improvers – number of women who met clinically important improvements on the FACT-B+4 scores (≥ 8 points) from baseline to 12 months post-surgery.
2. ICERs are calculated as the incremental total cost divided by the incremental improvers
3. ICERs are calculated as incremental mean cost divided by incremental mean QALYs

Table 4: Results of sensitivity analyses on incremental cost per effects (AU\$ 2014)

	Private EP model		Service provider model	
	Improvers	QALYs	Improvers	QALYs
Base case	\$2,282	\$90,842	\$2,644	\$105,231
QALY Low 95% CI (intervention group) 0.824	n/a	UC dominates ¹	n/a	UC dominates ¹
QALY High 95% CI (intervention group) 0.863	n/a	\$26,374	n/a	\$30,551
QALY Low 95% CI (UC group) 0.797	n/a	\$16,685	n/a	\$19,328
QALY High 95% CI (UC group) 0.877	n/a	UC dominates ¹	n/a	UC dominates ¹
Leasing small car AU\$63.54 / fortnight	n/a	n/a	\$2,606	\$103,733
Leasing larger car AU\$116.14 / fortnight	n/a	n/a	\$2,680	\$106,656
Provider model costs 30% higher AU\$1257	n/a	n/a	\$3,454	\$137,475
Provider model costs 30% lower AU\$880	n/a	n/a	\$1,834	\$95,559
UC group out of pockets 25% of intvn group	\$2,311	\$91,966	\$2,672	\$106,355
UC group out of pockets 75% of intvn group	\$2,254	\$89,718	\$2,616	\$104,107
UC group out of pockets 100% of intvn group	\$2,226	\$88,594	\$2,587	\$102,983
Incremental number of improvers – 30% higher	\$1,756	n/a	\$2,034	n/a
Incremental number of improvers – 30% lower	\$3,261	n/a	\$3,777	n/a

CI = confidence interval, EP = exercise physiologist, QALYs = quality-adjusted life years, UC = usual care group, intvn - intervention

1. Dominates = lower cost and higher QALYs. QALY values in these sensitivity analyses are the post-intervention unmodelled 95% CI values.