

Real-world patient- and caregiver-reported outcomes in advanced breast cancer

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ABSTRACT

Background Advanced breast cancer (ABC) represents a substantial burden for patients and caregivers. In the present study, we aimed to estimate quality of life (QOL), utility, productivity loss, pain, health care resource utilization, and costs for patients with ABC, and QOL, utility, and productivity loss for their caregivers.

Methods This multicentre prospective non-interventional study was conducted in Canada. Eligible participants were postmenopausal women with estrogen receptor-positive, HER2-negative unresectable ABC and their caregivers. Validated questionnaires were used to measure QOL, utility, productivity loss, and pain. Patients and caregivers were classified into 4 health states typically used in oncology economic modelling: first-line progression-free (1L-PF), first-line progressive disease (1L-PD), second- or subsequent-line progression-free (≥ 2 L-PF), and second- or subsequent-line progressive disease (≥ 2 L-PD).

Results Most patients and caregivers accepted to participate, with total recruitment of 202 patients and 78 caregivers. Compared with patients in PF, patients in PD had lower mean QOL scores (52.9 ± 29.9 for 1L-PD vs. 68.2 ± 23.2 for 1L-PF, and 54.0 ± 23.6 for ≥ 2 L-PD vs. 66.0 ± 22.1 for ≥ 2 L-PF), lower mean utility values (0.64 ± 0.22 for 1L-PD vs. 0.73 ± 0.20 for 1L-PF, and 0.65 ± 0.25 for ≥ 2 L-PD vs. 0.74 ± 0.18 for ≥ 2 L-PF), and greater productivity loss (39.4 ± 27.7 for 1L-PD vs. 27.5 ± 30.1 for 1L-PF, and 37.6 ± 29.2 for ≥ 2 L-PD vs. 32.0 ± 29.0 for ≥ 2 L-PF). Compared with caregivers of patients in PF, caregivers of patients in PD had lower QOL scores and utility values, and greater productivity loss.

Conclusions Study results indicate that, for patients and caregivers, PD health states are associated with a deterioration of QOL and utility and a decrease in productivity in both 1L and ≥ 2 L.

Key Words Real-world evidence, advanced breast cancer, patient-reported outcomes, caregivers, quality of life, utility, productivity losses, health care resource utilization

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BACKGROUND

In Canada, breast cancer (BCa) is the most frequently diagnosed cancer and the 2nd greatest cause of cancer-related death in women. In 2016, approximately 25,700 Canadian women were diagnosed with BCa, and about 5000 died from their disease¹. Advanced BCa (ABC), which comprises both unresectable locally advanced BCa and metastatic BCa, is an incurable disease whose 5-year survival rate is about 25%². Treatments for ABC aim to improve or maintain quality of life (QOL), delay disease progression, and possibly extend survival³. Systemic treatment options for patients with

ABC include hormonal therapy, chemotherapy, and targeted therapy^{2,4}. Despite 65%–70% of BCas being estrogen receptor-positive (ER+) and HER2-negative (HER2-), treatments that specifically target this subtype are limited in number⁵. Hence, additional effective therapies are needed⁶.

In Canada and many European countries, the integration of innovations into the health care system is closely linked with the reimbursement decisions of public payers. Although therapeutic value is a key component in those decisions, health technology assessment (HTA) agencies also consider the cost-effectiveness of innovations, which is estimated by means of economic evaluations. In addition,

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HTA agencies are increasingly concerned about the effects of new therapies on other outcomes such as QoL, work productivity, and activity impairment for patients and their caregivers. That patient-centred approach explains the growing interest in patient-reported outcomes and the preferred choice of HTA agencies for cost-utility analyses from among the various types of economic evaluations. Cost-utility analyses evaluate an intervention and its comparator in terms of life expectancy and patient preferences for various health outcomes.

Although patient-reported outcomes have gained prominence in randomized controlled trials, the strict eligibility criteria in such trials mean that results are rarely generalizable to a broader population. Thus, HTA agencies are increasingly seeking real-world evidence to support their decisions⁷. To this day, real-world evidence of patient-reported outcomes in ABC that could be used by HTA agencies is scarce⁸. Consequently, the primary objective of the present study was to estimate, in a real-world setting, QoL, utility, productivity losses, pain, health care resource utilization, and costs for postmenopausal patients with ER+ HER2- ABC. A secondary objective was to estimate the utility, QoL, and productivity losses of caregivers.

METHODS

Study Design and Participants

This prospective observational study was conducted in 5 major oncology centres in the provinces of Quebec and Ontario. Participants enrolled in the study were postmenopausal women diagnosed with ABC with confirmed ER+ HER2- status, and their caregivers. Participants were recruited during a follow-up visit with the treating oncologist at any point during the course of their disease. The recruitment objective was 200 patients, and patients were recruited until that limit was reached. If a caregiver accompanied the patient, the caregiver was asked about their interest in participating in the caregiver part of the study.

Data Sources

Data collected during the study were the characteristics of patients and caregivers, the medical condition of the patients, ABC-related treatments and treatment response, and patient- and caregiver-reported outcomes. Data collection was performed using questionnaires and case-report forms. Paper questionnaires were answered directly by patients and caregivers; the case-report forms were completed by study personnel at each site using the patient's medical file. Study data were collected at recruitment and at 3 months and 6 months later. The first set of questionnaires was completed at the hospital; subsequent questionnaires were sent to the patient's home.

Health States

Health states were defined according to the patient's line of treatment and disease status at recruitment. Line of treatment was categorized as either first line (1L) or second and subsequent lines (≥ 2 L). Disease status was categorized as either progression-free (PF) or progressive disease (PD), which are the states typically used in economic modeling in oncology. The PF status was defined as complete

response, partial response, or stable disease, and the PD status was defined as disease progression, established by the treating oncologists according to current clinical practice. Disease status was determined within 90 days of recruitment because the date of recruitment did not necessarily coincide with a date of disease assessment (for example, imaging). The 90-day period was selected because that is the usual time between disease assessments for patients in progression. Hence, patients and associated caregivers were classified into 4 mutually exclusive health states: 1L-PF, 1L-PD, ≥ 2 L-PF, and ≥ 2 L-PD.

Outcome Measures

QoL

The health-related QoL of patients was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30-question core Quality of Life Questionnaire (QLQ-C30) and its BCa module, the EORTC QLQ-BC23. Those instruments have been validated and shown to be reliable in multicultural clinical research settings⁹. The QLQ-C30 consists of 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea or vomiting), and a global health status (QoL) scale. A number of single items also allow for the assessment of additional symptoms commonly reported by cancer patients such as dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. The 23-item EORTC QLQ-BC23 allows for an assessment of functional scales (body image, sexual functioning, sexual enjoyment, and future perspective) and symptom scales (side effects of systemic therapy, breast symptoms, arm symptoms, and upset because of hair loss) in patients diagnosed with BCa. The QLQ tools provide a specific score ranging from 0 to 100 for each scale measured. A high score for a functional scale represents a high or healthy level of functioning, a high score for global health status represents high QoL, but a high score for a symptom scale represents a high level of symptomatology or problems¹⁰.

For caregivers, QoL was measured using the CareGiver Oncology Quality of Life questionnaire, a validated instrument consisting of 29 items that allow for the assessment of 10 dimensions: psychological well-being, burden, relationship with health care, administration and finances, coping, physical well-being, self-esteem, leisure time, social support, and private life. A score specific to each dimension is provided. A summary index value capturing all the dimensions can also be calculated. Scores range from 0 to 100, with a higher score being associated with better QoL¹¹.

Utility

The EQ-5D-5L questionnaire, developed by the EuroQol Research Foundation (Rotterdam, Netherlands), was used to collect utility values for the patients with ABC and for their caregivers. This validated instrument is widely used and allows for an assessment of 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), which are themselves each composed of 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems).

The questionnaire also includes a visual analog scale (VAS) that uses a vertical scale ranging from 0 to 100, with endpoints labelled “the best health you can imagine” and “the worst health you can imagine” to record the respondent’s self-rated health^{12,13}.

Productivity Loss

The Work Productivity and Activity Impairment (WPAI) questionnaire [Specific Health Problem (Cancer)] was used to assess the work productivity loss and activity impairment percentages attributable to ABC for patients and their caregivers. Work productivity loss includes absenteeism (the period of absence from work) and presenteeism (the reduction of productivity while at work). Activity impairment is the percentage of activity impairment attributable to ABC. An adapted form completed by the caregivers assessed the effects on their productivity of caring for a patient with ABC. Higher percentages indicate greater productivity loss and greater activity impairment¹⁴.

Pain

The Brief Pain Inventory (BPI) short-form 9-item questionnaire was used to assess pain in the patients with ABC. The questionnaire is designed to assess pain severity and pain interference with daily functioning in various diseases, including cancer. Pain associated with ABC was described using the pain severity and pain interference scores. The score for both scales ranges from 0 to 10, where a higher score is associated with a worse level of pain¹⁵.

Resource Utilization

A 6-item questionnaire was used to capture health care resource utilization—including hospitalizations, emergency and medical visits, diagnostic procedures (laboratory tests, imaging, and biopsies), home nursing, and informal care—by the patient over a 3-month period. Health care resource utilization excluded medication. Data retrieved from this questionnaire reflected the patient’s perspective about resource utilization during the preceding 3-month period. Associated costs in Canadian dollars were also estimated by using the OHIP (Ontario Health Insurance Plan) schedule of fees for physician services and laboratory services, the Ontario Case Costing Initiative database, the Régie de l’assurance maladie du Québec schedule of fees, and other government publications.

Data Analysis

Analysis and handling of missing data for the QLQ-C30, QLQ-BR23, CareGiver Oncology Quality of Life, EQ-5D-5L, and WPAI questionnaires accorded with the scoring guide for each instrument^{11,16–18}. Patient and caregiver characteristics are reported by the health state of the patient (1L-PF, 1L-PD, ≥ 2 L-PF, or ≥ 2 L-PD). Patient and caregiver QOL, utility, and productivity losses, and patient pain and health care resource utilization are also reported by health state. Health care resource utilization is presented in terms of the mean number of resources used monthly per patient and the mean cost incurred monthly per patient (with standard deviation). Categorical variables are summarized in frequency tables (number and proportion), and descriptive statistics (mean and standard deviation) are provided for

continuous variables. Because our study was observational and descriptive, and no statistical tests were intended, no formal sample size calculation was performed. The sample size was established to ensure both generalizability of the results and feasibility of the study in a reasonable timeframe. Data analyses were performed in the IBM SPSS Statistics software application (version 24.0: IBM, Armonk, NY, U.S.A.).

Ethics Considerations

The study (registered with <http://ClinicalTrials.gov> as NCT02315365) was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board at each participating centre. Each patient had to sign and date an informed consent form before participating to the study.

RESULTS

Patients and Disease Characteristics

Table 1 presents patient and disease characteristics. Between March 2015 and June 2016, 202 patients were recruited. Of those 202, 67 were in 1L-PF, 17 were in 1L-PD, 89 were in ≥ 2 L-PF, and 29 were in ≥ 2 L-PD. Of the 118 patients in ≥ 2 L at recruitment, 46 (39.0%), 28 (23.7%), 19 (16.1%), 10 (8.5%), 7 (5.9%), 4 (3.4%), 3 (2.5%), and 1 (0.8%) were in their second, third, fourth, fifth, sixth, seventh, eighth, and eleventh line of treatment respectively. Mean age at recruitment ranged between 60 and 66 years in the various health states and was slightly lower for patients in 1L-PD than for those in other health states. In all health states, most patients were married or had a common-law partner, and most patients were retired. The mean duration from ABC diagnosis to recruitment ranged between 1.6 and 4.6 years in the various health states and was, as expected, greater for patients in ≥ 2 L than for patients in 1L. In all health states, bone was the most frequent site of metastasis. The proportion of patients with 3 or more sites of metastasis was higher in PD than in PF. At recruitment, most patients in 1L were treated with hormonal therapy only, and most patients in ≥ 2 L were receiving chemotherapy only.

Patient-Reported Outcomes

Table 2 presents patient-reported outcomes by health state.

QOL

The mean global health score on the QLQ-C30 questionnaire indicated that QOL was lower for patients in PD than for patients in PF regardless of line-of-treatment group (52.9 ± 29.9 in 1L-PD vs. 68.2 ± 23.2 in 1L-PF, and 54.0 ± 23.6 in ≥ 2 L-PD vs. 66.0 ± 22.1 in ≥ 2 L-PF). All values for the functional and symptom scales of the QLQ-C30 can be found in the online supplementary material (Table SM-I).

Overall, fatigue was the symptom scale having the most negative effect on patient QOL, with the greatest effect reported by patients in PD (compared with patients in PF). Results of the QLQ-BR23 showed that, in all health states, the functional scale most affected was sexual functioning. All values for the functional and symptom scales of the QLQ-BR23 can be found in the online supplementary material (Table SM-II).

TABLE I Characteristics of the study patients

Characteristic	Line of treatment			
	First		Second and subsequent	
	PF	PD	PF	PD
Patients (n)	67	17	89	29
Female sex [n (%)]	67 (100.0)	17 (100.0)	89 (100.0)	29 (100.0)
Mean age (years)	66±10	60±10	64±10	64±9
Ethnicity [n (%)]				
White	64 (95.5)	16 (94.1)	88 (98.9)	29 (100.0)
Other	2 (3.0)	1 (5.9)	1 (1.1)	0 (0.0)
Missing	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Smoking status [n (%)]				
Current smoker	9 (13.4)	1 (5.9)	8 (9.0)	5 (17.2)
Ex-smoker	25 (37.3)	6 (35.3)	33 (37.1)	14 (48.3)
Never smoked	33 (49.3)	10 (58.8)	47 (52.8)	10 (34.5)
Missing	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Marital status [n (%)]				
Single	8 (11.9)	3 (17.6)	17 (19.1)	4 (13.8)
Married or common-law	41 (61.2)	9 (52.9)	44 (49.4)	17 (58.6)
Divorced	9 (13.4)	2 (11.8)	17 (19.1)	8 (27.6)
Widowed	9 (13.4)	2 (11.8)	10 (11.2)	0 (0.0)
Missing	0 (0.0)	1 (5.9)	1 (1.1)	0 (0.0)
Highest education level [n (%)]				
Elementary	4 (6.0)	0 (0.0)	5 (5.6)	1 (3.4)
High school	31 (46.3)	12 (70.6)	43 (48.3)	8 (27.6)
College	13 (19.4)	3 (17.6)	22 (24.7)	13 (44.8)
University	19 (28.4)	2 (11.8)	18 (20.2)	7 (24.1)
Missing	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Employment status [n (%)]				
Active, full-time	7 (10.4)	0 (0.0)	6 (6.7)	3 (10.3)
Active, part-time	5 (7.5)	3 (17.6)	14 (15.7)	1 (3.4)
Retired	44 (65.7)	8 (47.1)	47 (52.8)	20 (69.0)
Unemployed	2 (3.0)	2 (11.8)	7 (7.9)	1 (3.4)
Invalid	6 (9.0)	4 (23.5)	7 (7.9)	2 (6.9)
Other	1 (1.5)	0 (0.0)	6 (6.7)	2 (6.9)
Missing	2 (3.0)	0 (0.0)	2 (2.2)	0 (0.0)
Participation of a caregiver [n (%)]	27 (40.3)	6 (35.3)	33 (37.1)	12 (41.4)
Receptor status [n (%)]				
HER2-negative	67 (100.0)	17 (100.0)	89 (100.0)	29 (100.0)
ER-positive	67 (100.0)	17 (100.0)	89 (100.0)	29 (100.0)
PgR-negative	8 (11.9)	3 (17.6)	9 (10.1)	3 (10.3)
PgR-positive	59 (88.1)	13 (76.5)	80 (89.9)	25 (86.2)
PgR unknown	0 (0.0)	1 (5.9)	0 (0.0)	1 (3.4)
Mean duration since ABC Dx (years)	1.6±2.1	1.3±1.1	4.4±3.2	4.6±3.8
Metastasis site [n (%)]				
Bone	45 (67.2)	12 (70.6)	72 (80.9)	25 (86.2)
Lung	16 (23.9)	6 (35.3)	33 (37.1)	15 (51.7)
Liver	10 (14.9)	2 (11.8)	35 (39.3)	12 (41.4)
Lymph nodes	16 (23.9)	5 (29.4)	23 (25.8)	11 (37.9)
Other	16 (23.9)	4 (23.5)	22 (24.7)	9 (31.0)

TABLE I Continued

Characteristic	Line of treatment			
	First		Second and subsequent	
	PF	PD	PF	PD
Metastasis burden [n (%)]				
<3 Sites	61 (91.0)	13 (76.5)	64 (71.9)	15 (51.7)
≥3 Sites	6 (9.0)	4 (23.5)	25 (28.1)	14 (48.3)
Treatment at recruitment [n (%)]				
Chemotherapy	12 (17.9)	2 (11.8)	45 (50.6)	16 (55.2)
Hormonal therapy	48 (71.6)	13 (76.5)	35 (39.3)	7 (24.1)
Chemotherapy and hormonal therapy	1 (1.5)	0 (0.0)	1 (1.1)	2 (6.9)
Targeted therapy and hormonal therapy	4 (6.0)	2 (11.8)	5 (5.6)	2 (6.9)
None	2 (3.0)	0 (0.0)	3 (3.4)	2 (6.9)

PF = progression-free; PD = progressive disease; HER2 = human epidermal growth factor receptor 2; ER = estrogen receptor; PgR = progesterone receptor; ABC = advanced breast cancer; Dx = diagnosis.

TABLE II Patient-reported outcomes

Outcome	Line of treatment			
	First		Second and subsequent	
	PF	PD	PF	PD
Patients (n)	67	17	89	29
Quality of life				
Global health status (mean score)	68.2±23.2	52.9±29.9	66.0±22.1	54.0±23.6
Utility				
Mean utility value	0.73±0.20	0.64±0.22	0.74±0.18	0.65±0.25
Mean VAS	76.8±19.0	66.2±21.2	71.7±21.0	66.1±23.1
Productivity loss				
Patients currently employed [n (%)]	9 (13.4)	3 (17.6)	18 (20.2)	4 (13.8)
Mean productivity loss (%) ^a	30.9±29.4	33.3±30.6	9.5±18.6	40.0±39.3
Mean activity impairment (%)	27.5±30.1	39.4±27.7	32.0±29.0	37.6±29.2
Pain				
Mean pain severity score	2.4±2.4	3.5±2.3	2.5±2.1	2.5±2.1
Mean pain interference score	2.0±2.0	3.1±2.2	2.0±2.1	2.6±2.2

^a For employed patients only.

PF = progression-free; PD = progressive disease; VAS = visual analog scale.

Utility

As presented in Table II, utility values were lower in PD than in PF in both line-of-treatment groups (0.64 ± 0.22 in 1L-PD vs. 0.73 ± 0.20 in 1L-PF, and 0.65 ± 0.25 in ≥2L-PD vs. 0.74 ± 0.18 in ≥2L-PF). The same trend was observed for the VAS values. Results also show that the most frequent problem reported by patients with ABC was pain or discomfort (supplementary Table SM-III).

Productivity Loss

The numbers of employed patients during the study were 9 (13.4%), 3 (17.6%), 18 (20.2%), and 4 (13.8%) in 1L-PF, 1L-PD, ≥2L-PF, and ≥2L-PD respectively. Results indicate that the percentages of work productivity loss in 1L were similar for both PF and PD (30.9% ± 29.4% and 33.3% ± 30.6% respectively

Table II). For patients in ≥2L, the percentage of work productivity loss was much greater in PD than in PF (40.0% ± 39.3 vs. 9.5% ± 18.6). The activity impairment percentage was higher for patients in PD than for patients in PF in both 1L and ≥2L (39.4% ± 27.7% in 1L-PD vs. 27.5% ± 30.1% in 1L-PF, and 37.6% ± 29.2% in ≥2L-PD vs. 32.0% ± 29.0 in ≥2L-PF).

Pain

The pain severity score for 1L patients was higher in PD than in PF (3.5 ± 2.3 vs. 2.4 ± 2.4 respectively, Table II). However, for ≥2L patients, pain severity scores were similar (2.5 ± 2.1 in PD and 2.5 ± 2.1 in PF). Compared with patients in PF, patients in PD reported a higher pain interference score (3.1 ± 2.2 in 1L-PD vs. 2.0 ± 2.0 in 1L-PF, and 2.6 ± 2.2 in ≥2L-PD vs. 2.0 ± 2.1 in ≥2L-PF).

Health Care Resource Utilization and Costs

Table III presents health care resource utilization and costs, which includes hospitalizations, emergency department and medical visits, diagnostic procedures (laboratory tests, imaging, and biopsies), home nursing, and informal care. Medication was excluded. The mean cost for 1L patients was higher in PF than in PD (CA\$2,949 ± CA\$8,450 vs. CA\$2,405 ± CA\$3,389 respectively). However, the opposite trend was observed for ≥2L patients (CA\$1,592 ± CA\$2,075 in PD vs. CA\$1,057 ± CA\$1,275 in PF).

Caregiver Characteristics

Table IV presents characteristics for the 78 caregivers included in the study. Of those 78 caregivers, 27, 6, 33, and 12 were caring for patients in 1L-PF, 1L-PD, ≥2L-PF, and ≥2L-PD respectively. Except in 1L-PD, most caregivers were men. Mean age at recruitment ranged between 40 and 64 years in the various health states and was lower in 1L-PD than in the other health states. Except in 1L-PD, most caregivers were the patient's spouse. In all health states, most caregivers were retired.

Caregiver-Reported Outcomes

Table V presents caregiver-reported outcomes by health state.

CareGiver Oncology Quality of Life

In 1L, QOL was lower for caregivers of patients in PD than for caregivers of patients in PF (52.9 ± 15.7 in PD vs. 71.3 ± 11.3 in PF, Table V). However, for ≥2L, QOL of caregivers was similar in both PF and PD (73.2 ± 13.2 in PF and 72.5 ± 10.7 in PD). Results of all dimensions of the CareGiver Oncology Quality of Life are presented in supplementary Table SM-IV.

Utility

Caregiver utility values were lower in PD than in PF (0.66 ± 0.30 in 1L-PD vs. 0.82 ± 0.15 in 1L-PF, and 0.77 ± 0.21 in ≥2L-PD vs. 0.83 ± 0.11 in ≥2L-PF, Table V). In 1L, the mean VAS value was lower for caregivers of patients in PD than for caregivers of patients in PF. However, in ≥2L, VAS values were similar. Results also showed that the most frequent problem reported by caregivers was anxiety or depression (supplementary Table SM-V).

Productivity Loss

The numbers of employed caregivers during the study were 8 (29.6%), 2 (33.3%), 14 (42.4%), and 6 (50.0%) for 1L-PF, 1L-PD, ≥2L-PF, and ≥2L-PD respectively. In 1L, the percentage of productivity loss was greater in PD than in PF (52.3% ± 17.4% in PD vs. 25.9% ± 26.3% in PF, Table V). In ≥2L, the percentage work productivity loss was similar in the PF and PD groups.

TABLE III Health care resource utilization and cost associated with advanced breast cancer management in a 3-month period

Health care resource	Line of treatment			
	First		Second and subsequent	
	PF	PD	PF	PD
Patients (n)	67	17	89	29
Hospitalization days				
Mean use (n)	1.7±7.9	1.3±3.0	0.2±1.0	0.7±1.9
Mean cost (CA\$)	1,650±7,762	1,292±2,957	192±959	729±1,843
Emergency visits				
Mean use (n)	0.3±0.8	1.1±2.2	0.2±0.5	0.4±0.9
Mean cost (CA\$)	54±130	182±363	28±79	69±142
Medical visits ^a				
Mean use (n)	3.6±3.5	4.1±2.7	3.9±4.3	4.3±2.7
Mean cost (CA\$)	12±21	16±25	6±14	12±23
Medical procedures ^b				
Mean use (n)	2.3±2.0	2.3±1.8	2.8±3.1	2.9±1.5
Mean cost (CA\$)	87±75	88±68	106±119	109±58
Home nursing				
Mean use (n)	0.1±0.3	0.1±0.3	0.2±0.4	0.1±0.3
Mean cost (CA\$)	4±10	4±11	6±12	2±8
Informal care				
Mean use (n)	0.4±0.5	0.4±0.5	0.4±0.5	0.5±0.5
Mean cost (CA\$)	56±74	67±78	64±76	82±78
Mean total cost (CA\$)	2,949±8,450	2,405±3,389	1,057±1,275	1,592±2,075

^a Breast cancer–related medical visits with general practitioner, oncologist, and other specialists.

^b Breast cancer–related imaging tests, laboratory tests, biopsies, and other medical procedures.

PF = progression-free; PD = progressive disease.

TABLE IV Characteristics of the caregivers

Characteristic	Patient's line of treatment			
	First		Second and subsequent	
	PF	PD	PF	PD
Caregivers (<i>n</i>)	27	6	33	12
Sex [<i>n</i> (%)]				
Women	4 (14.8)	5 (83.3)	13 (39.4)	2 (16.7)
Men	23 (85.2)	1 (16.7)	20 (60.6)	10 (83.3)
Mean age (years)	61±14	40±27	61±12	64±18
Marital status [<i>n</i> (%)]				
Single	4 (14.8)	2 (33.3)	6 (18.2)	1 (8.3)
Married/common-law	23 (85.2)	3 (50.0)	22 (66.7)	10 (83.3)
Divorced	0 (0.0)	0 (0.0)	3 (9.1)	0 (0.0)
Widowed	0 (0.0)	1 (16.7)	2 (6.1)	1 (8.3)
Highest education level [<i>n</i> (%)]				
Elementary	1 (3.7)	1 (16.7)	0 (0.0)	0 (0.0)
High school	11 (40.7)	3 (50.0)	11 (33.3)	2 (16.7)
College	6 (22.2)	1 (16.7)	7 (21.2)	6 (50.0)
University	9 (33.3)	1 (16.7)	15 (45.5)	4 (33.3)
Employment status [<i>n</i> (%)]				
Active, full time	6 (22.2)	2 (33.3)	13 (39.4)	5 (41.7)
Active, part time	1 (3.7)	0 (0.0)	2 (6.1)	1 (8.3)
Retired	18 (66.7)	3 (50.0)	17 (51.5)	6 (50.0)
Unemployed	1 (3.7)	0 (0.0)	1 (3.0)	0 (0.0)
Invalid	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Other	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
Relationship to patient [<i>n</i> (%)]				
Spouse	20 (74.1)	1 (16.7)	19 (57.6)	8 (66.7)
Parent	5 (18.5)	3 (50.0)	6 (18.2)	4 (33.3)
Child	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Sibling	1 (3.7)	0 (0.0)	5 (15.2)	0 (0.0)
Friend	0 (0.0)	1 (16.7)	2 (6.1)	0 (0.0)
Other	1 (3.7)	0 (0.0)	1 (3.0)	0 (0.0)

PF = progression-free; PD = progressive disease.

(33.1% ± 23.4% in PF and 30.8% ± 39.0% in PD). In 1L, the activity impairment percentage was higher for caregivers of patients in PD than for caregivers of patients in PF (55.0% ± 30.8% in PD vs. 23.1% ± 22.6% in PF). However, that difference was less important in ≥2L (25.8% ± 22.3% in PD vs. 21.8% ± 23.1% in PF).

DISCUSSION

The present study was designed to assess, in a real-world setting, QOL, utility, productivity losses, pain, and health care resource utilization for postmenopausal patients with ER+ HER2–ABC. It was also designed to assess QOL, utility, and productivity losses of caregivers caring for an ABC patient.

Results indicate that, for both line-of-treatment groups, QOL and utility were lower for patients in PD than for patients in PF. Results also suggest that work productivity loss was

greater for patients in PD than for those in PF, and that the difference was more important in ≥2L. However, given the limited number of employed patients, those results should be interpreted with caution. Because the productivity of an individual does not limit itself to work-related productivity, activity impairment is often the preferred outcome in health economics and outcomes research studies. Results presented here indicate that, for both line-of-treatment groups, the percentages of activity impairment were greater in PD than in PF.

Results of the BPI questionnaire indicated that pain interference was greater for patients in PD than for those in PF. That trend was also observed for pain severity in 1L patients but not in ≥2L patients, whose pain severity scores were similar whether in PD or PF. Overall, a considerable number of resources were consumed. For 1L patients, the total mean cost was higher in PF than in PD. For ≥2L patients, the opposite trend was observed: the mean cost was higher

TABLE V Caregiver-reported outcomes

Outcome	Patient's line of treatment			
	First		Second and subsequent	
	PF	PD	PF	PD
Caregivers (<i>n</i>)	27	6	33	12
Quality of life				
Mean index value	71.3±11.3	52.9±15.7	73.2±13.2	72.5±10.7
Utility				
Mean utility value	0.82±0.15	0.66±0.30	0.83±0.11	0.77±0.21
Mean VAS	81.8±12.3	70.8±18.0	84.4±12.4	83.1±12.5
Productivity loss				
Caregivers currently employed [<i>n</i> (%)]	8 (29.6)	2 (33.3)	14 (42.4)	6 (50.0)
Mean work productivity loss (%) ^a	25.9±26.3	52.3±17.4	33.1±23.4	30.8±39.0
Mean activity impairment (%)	23.1±22.6	55.0±30.8	21.8±23.1	25.8±22.3

^a For employed caregivers only.

PF = progression-free; PD = progressive disease; VAS = visual analog scale.

in PD than in PF. Those observations could be explained by the fact that hospitalizations are a cost-driver, and hospitalizations occurred more often in PF than in PD for 1L patients and more often in PD than in PF for ≥2L patients. The present study also indicates that QOL, utility, and productivity loss were worse for caregivers of 1L patients in PD than for those of 1L patients in PF. Looking at caregivers of ≥2L patients, results indicate that QOL, utility, and productivity loss were similar in the PF and PD groups.

Utility values reported here are similar to values obtained by van Kampen *et al.*⁸, who conducted a real-world study and who also used the EQ-5D questionnaire to assess utility values according to the PF and PD health states. No study found in the literature evaluated QOL, productivity loss, activity impairment, pain, or resource utilization by the PF or PD health states.

To our knowledge, the present real-world study is the first in Canada to have been specifically designed to evaluate health economic outcomes associated with ER+HER2–ABC according to the health states typically used in economic models. Results presented here will provide data for economic evaluations of new treatments in ABC. The data concerning utility and productivity losses will allow for the conduct of cost–utility analyses from a societal perspective. Furthermore, validated questionnaires were used to assess QOL, utility, productivity loss, and pain. In addition, health state allocation was based on the treating oncologist's opinion rather than on the predefined criteria usually used in clinical trials, thus reflecting real-world clinical practice. Despite the crucial role of relatives in caring for patients, the effect of the disease on the lives of caregivers is rarely documented. Hence, our study also allowed for the measurement of the effect of a patient's health state on their caregiver's QOL, utility, and productivity loss.

Our study has limitations that must be considered. First, as in all studies with this type of design, self-selection bias (which arises when a subgroup of the study population is more or less inclined to participate) might have occurred. In our case, it is possible that healthier patients might

have been more inclined to participate. Consequently, the entire ABC population might not be reflected, and our results might not be generalizable to the 4 health states. Also, the process of patient selection was not systematically kept at each site, limiting the possibility of estimating the participation rate. A high rate of participation would have minimized the self-selection bias. Second, the 90-day window that was used to establish health state in the participating patients might have led to information bias, which is defined as the misclassification of patient exposure. Indeed, because patients were asked to complete the set of questionnaires at recruitment, which did not necessarily coincide with the date of disease assessment, it is possible that patients who progressed within the 90-day period were in fact not progressing at recruitment. However, because clinical guidelines in ABC recommend that evaluation of response to therapy should take place every 2–4 months for patients receiving hormonal therapy or after 2 or 4 cycles of chemotherapy, the 90-day period that was used to establish health state might be considered a reasonable timeframe. It should be noted that health care resource utilization was based on each patient's memory and comprehension of medical services rendered. Resource utilization and costs are therefore most probably underestimated. Nonetheless, the resource questionnaire was constructed to minimize the effect of recall bias on cost by asking patients about resource utilization in the 3 months preceding questionnaire administration. A literature search has evaluated the accuracy of self-reported health care utilization at 60% for a recall period of 3 months, 36% for a period of 6 months, and 20% for a period of 12 months¹⁹. Moreover, cost of treatment was not included in the analysis, thus not reflecting the entire burden associated with the management of ABC. Finally, because no statistical tests were performed, observations about differences between the groups of patients and caregivers are solely for descriptive purposes. The sample sizes in the PD health states also limit the insight to be obtained from the results. Results should therefore be interpreted by taking all limitations into consideration.

CONCLUSIONS

Real-world studies, such as the one presented here, allow for the collection of information complementary to clinical trials data, providing additional data about the potential humanistic and social effects of health innovations. Furthermore, real-world studies including caregivers allow for a better characterization of the overall effect of a disease or treatment, especially in oncology.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: MM, JL, PC, CP, and FC received research funds to conduct this study. GZ is an employee of Pfizer Inc. and owns Pfizer shares. TT is an employee of Pfizer Canada and owns Pfizer shares. JL received research funds from Pfizer Inc. to conduct this study.

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