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Cost-Effectiveness of Chemotherapy for Breast Cancer and Age Effect in Older Women

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ABSTRACT

Background: Previous economic evaluations compared specific chemotherapy agents using input parameters from clinical trials and resource utilization costs. Cost-effectiveness of treatment groups (drug classes) using community-level effectiveness and cost data, however, has not been assessed for elderly patients with breast cancer. **Objective:** To assess the cost-effectiveness of chemotherapy regimens by age and disease stage under "real-world" conditions for patients with breast cancer. **Methods:** The Surveillance Epidemiology and End Results-Medicare data were used to identify patients with breast cancer with American Joint Committee on Cancer stage I/II/IIIa, hormone receptor–negative (estrogen receptor–negative and progesterone receptor–negative) patients from 1992 to 2009. Patients were categorized into three adjuvant treatment groups: 1) no chemotherapy, 2) anthracycline, and 3) non–anthracycline-based chemotherapy. Median life-years and quality-adjusted life-years (QALYs) were measured using Kaplan-Meier analysis and were evaluated against average total health care costs (2013 US dollars). **Results:** A total of 4575 patients (propensity score–matched) were included for the primary analysis. The anthracycline group experienced 12.05 QALYs and mean total health care costs of $119,055, resulting in an incremental cost-effectiveness ratio of $7,688 per QALY gained as compared with the no chemotherapy group (QALYs 7.81; average health care cost $86,383). The non–anthracycline-based group was dominated by the anthracycline group with lower QALYs (9.56) and higher health care costs ($122,791). Base-case results were found to be consistent with the best-case and worst-case scenarios for utility assignments. Incremental cost-effectiveness ratios varied by age group (range $3,790–$90,405 per QALY gained). **Conclusions:** Anthracycline-based chemotherapy was found cost-effective for elderly patients with early stage (stage I, II, IIIa) breast cancer considering the US threshold of $100,000 per QALY. Further research may be needed to characterize differential effects across age groups.

Keywords: breast cancer, chemotherapy, cost-effectiveness, cost-utility.

Introduction

Analysts have called for economic evaluation of alternative treatment strategies for specific types of patients with breast cancer [1,2]. Previous research has examined the cost of treating breast cancer in the United States and the cost-effectiveness of alternative treatments, primarily associated with alternative drug regimens [3–5]. Economic evaluations of breast cancer treatment are often based on hypothetical cohorts and/or modeling of disease progression [4–9], in which health outcomes and costs are based on literature-derived parameters [4–9]. Age has rarely been examined as a factor in the assessment of cost-effectiveness of chemotherapy for patients with breast cancer [5]. Surveillance Epidemiology, End Results (SEER)-Medicare data have been used to estimate the cost of colorectal cancer treatment [10,11] but not to examine the cost-effectiveness of chemotherapy stratified by age group and stage of breast cancer. The present study advances the field by using a large, multiyear cohort to assess the cost-effectiveness of chemotherapy regimens by age and disease stage under "real-world" conditions for patients with breast cancer.

It is important to know whether the survival benefit associated with the administration of adjuvant chemotherapy in randomized clinical trials remains evident in community-based practices for elderly patients with breast cancer. Limited evidence exists (from clinical trials) for the benefit of chemotherapy in women 70 years or older with node-positive tumors or node-negative tumors of more than 1 cm [12–14]. The latest review [14] stated, "In subgroup analyses for trials of standard or near-standard cyclophosphamide, methotrexate, and fluorouracil

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versus no chemotherapy the proportional risk reduction appeared inversely related to age and nodal status, but again appeared independent of ER status." Their Web Appendix (Table P14) showed that the relative risk for mortality was 0.59 for women younger than 45 years, 0.66 for women aged 45 to 54 years, and 0.87 for women aged 55 to 69 years. In their study, the overall effect of chemotherapy in those 65 years or older combined was significant at 0.76 for mortality reduction. A significant age-chemotherapy interaction was clear.

Muss [15] and Muss et al. [16,17] reported on the efficacy of chemotherapy in older patients. In these studies, all patients were combined as 65 years or older versus younger than 65 years. Although the authors concluded that there was no association between age and disease-free survival, it was not clear that the efficacy of chemotherapy was the same in those aged 70 to 74 or 75 to 79 years as in those aged 65 to 69 years. A recent observational study found, however, that for women 80 years or older, adjuvant chemotherapy was not effective except in a few patients who received adriamycin-cyclophosphamide; the mortality risk was significantly reduced for those aged 80 to 84 years [18].

One explanation for no statistically significant chemotherapy-associated survival benefit for women with breast cancer aged 70 years or older is the small number of elderly patients enrolled in clinical trials. These results, however, are not consistent with findings for chemotherapy-associated survival benefits for older patients with ovarian, lung, and colon cancer where the number of elderly patients in clinical trials is also small [19–21]. The large number of cases in this study enables us to determine whether chemotherapy benefits patients in this population.

This study compare life-years saved and quality-adjusted life-years (QALYs) saved for three alternative treatment regimens (no chemotherapy, anthracycline [doxorubicin or epirubicin]-based chemotherapy, and non–anthracycline-based chemotherapy). With quality-of-life adjustments assigned for cancer stage, recurrence, and debilitating adverse effects, the study considers both the positive and negative outcomes of chemotherapy and contrasts these outcomes with total health care cost. SEER-Medicare data are valuable for studying cancer outcomes because chemotherapy drugs are among the few drugs that are covered by the Medicare program over the past two decades, thus allowing chemotherapy-specific cost-effectiveness analyses. The results of economic evaluations have important clinical implications for physicians treating patients with cancer, for developing clinical practice guidelines, and for identifying critical target areas to be tested in future clinical trials. The potential impact of the present study is significant for treating patients with breast cancer 65 years or older in at least 16 of the regions in the United States captured in SEER and potentially generalizable to other areas.

Methods

Data Source, Population, and Chemotherapy Regimens

The SEER-Medicare–linked data provide information on patient and tumor characteristics and resource utilization information in 65 years or older patients with cancer. Accuracy and validity of these data have previously been established [22]. Women 65 to 94 years old diagnosed with breast cancer as the first primary tumor without other primary tumors from January 1992 to December 2009 were included. Women were excluded if the diagnosis was based on autopsy, death certificate, or if they died within 90 days of diagnosis. Enrollment in both Medicare parts A and B without any health maintenance organization enrollment from the time of diagnosis to death or the end of the study (December 31, 2010) was required. A total of 14,610 women diagnosed with American Joint Committee on Cancer stage I, II, or III A who had undergone either breast-conserving surgery or mastectomy for estrogen receptor and progesterone receptor–negative tumors from 16 SEER areas were included.

Propensity score matching was conducted to reduce selection bias, which is inherent to observation studies. A propensity score of receiving chemotherapy for each treatment group was calculated using multinomial logistic regression [23]. We also applied the inverse probability of treatment weighting (IPTW) method that uses the inverse of probabilities estimated from multinomial logistic regression as a weight to obtain the population estimate; however, a major limitation of this approach is high sensitivity to these weights and hence the probabilities need to be estimated very well [24–26]. The probabilities are as good as the covariates used to estimate them, and the covariates available using large administrative databases such as SEER-Medicare data are limited. Thus, the propensity score matching approach was selected as the primary analysis and IPTW as the secondary analysis. Although precision may be improved by selecting variables on the basis of their association with outcomes irrespective of the exposure [27], variable selection was based on regression covariates that have been found to be associated with chemotherapy selection [28–30], and were available in our data (i.e., age, race, marital status, tumor stage, tumor size, node positive/negative, tumor grade, type of surgery, radiation, comorbidity score, socioeconomic status, region, and year of diagnosis). A 1:1:1 propensity score matching was performed using the nearest-neighbor method [31]. The algorithm matches two treatment groups simultaneously with the referent group (no chemotherapy). All matched pairs of patients were within the prespecified caliper distance of 0.05. Chi-square test and standardized difference were used to assess the balance of covariates between the treatment groups [32–34]. An effect size of less than 0.1 indicated negligible difference between comparison groups [33]. A lifetime time horizon with maximum follow-up until December 2010 was applied.

Patients were placed into three treatment groups—no chemotherapy, anthracycline-based chemotherapy, and non–anthracycline-based chemotherapy—on the basis of Medicare claim codes identified within 12 months following diagnosis. Anthracycline-based chemotherapy was defined using Healthcare Common Procedure Coding System codes for doxorubicin (J9000, J9001, J9010) and epirubicin (J9178). Non–anthracycline-based chemotherapy was defined using chemotherapy-associated codes except for epirubicin and doxorubicin (Healthcare Common Procedure Coding System codes 96400-96549, J9002-J9009, J9011-J9177, J9179-J9999, and Q0083-Q0085; *International Classification of Diseases, Ninth Revision, Clinical Modification* codes V58.1, V66.2, and V67.2; *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure code 9925) [35–37].

Effectiveness and Cancer Phases

Life-years and QALYs gained were the treatment outcomes. *Patient survival times* were defined as days from diagnosis to death or end of study and were categorized into three phases: initial, continuing, and terminal [38]. Health state utilities were obtained from the literature for assignment to the specific disease phase, for adjuvant chemotherapy receipt (with or without major adverse event), and for time since diagnosis and disease recurrence (Table 1) [39,40]. Health state utilities for the initial phase were based on the receipt of any chemotherapy and the severity of chemotherapy-related adverse events. Adverse events were evaluated as "moderate" or "severe" if they were reported in outpatient and inpatient claims, respectively [41]. Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.08.008 presents a detailed list of

Table 1 – Utility weights assigned to various disease phases in base-case and alternative scenarios*.

Treatment phase	Base-case scenario	Best-case scenario	Worst-case scenario
Initial phase (first year)			
No adjuvant chemotherapy	0.85	0.85	0.58
Adjuvant chemotherapy—no or moderate toxicity	0.78		
Adjuvant chemotherapy—severe toxicity	0.58		
Continuing phase			
Stage I—year 2–5	0.91	0.99	0.84
Stage I—year 6+	0.99		
Stage II—year 2+	0.87		
Stage III—year 2+	0.84		
Recurrence	NA	NA	0.58
Terminal phase (last year of life)	0.23	0.3	0.16

NA, not applicable.
* Utility values were obtained from the literature [38,39].

adverse events. To ensure that the adverse events were related to chemotherapy, the initial phase was subdivided into four 3-month subphases and a patient was considered to have an adverse event during the subphase if at least one claim for a chemotherapy adverse event was reported in that subphase. Continuing phase utilities were based on breast cancer stage and time since diagnosis. In an alternate scenario (worst case) for the continuing phase, a recurrence was identified if there was a gap in chemotherapy for more than 4 months (± 15 days) in the continuing phase and a recurrence utility was assigned for the remaining continuing phase [42].

QALYs for each phase were computed by multiplying the phase survival time with the associated utility, and total QALYs were calculated by summing phase-specific QALYs. A nonparametric Kaplan-Meier analysis was conducted to obtain median life-years and QALYs. In our preliminary analysis, mean effectiveness was estimated but we were unable to generate survival bootstrap replicates for computing confidence intervals for the mean. Median effectiveness was selected, consistent with previous economic evaluations [43,44], and is more often used in survival studies [45]. A 3% annual discount rate was applied to life-years and QALYs. Similar analyses were conducted for alternative scenarios 1) best case: using the most optimistic utility value and 2) worst case: using the most conservative utility value (Table 1) and for age groups (65–69, 70–74, 75–79, and 80+ years). For the age group 65 to 69 years, median survival was not observed; therefore, parametric regression was used to estimate the median life-years and median QALYs. Log-normal distribution was used for the parametric regression as the best fit for the data when compared with weibull, log logistic, and exponential distribution using the Akaike information criterion [46].

Cost Analysis

Medicare amount paid for each claim was used to represent a US national payer perspective for health care costs. Total health care costs and phase-specific costs per month were estimated from diagnosis until death or end of study using claims for inpatient services, outpatient visits and procedures, physician services, skilled nursing facility, hospice, and durable medical equipment. Total health care cost for each patient was calculated by dividing the patient time into initial, continuing, and terminal phases. Costs incurred during each of these phases were aggregated to obtain phase-specific costs, which were summed to obtain the total health care cost for each patient. The effect of censoring on the cost estimates and incremental cost-effectiveness ratios (ICERs) was addressed in a sensitivity analysis by assigning age-specific median survival to patients who had not died by the end of study, and for the unobserved time (i.e., age-specific median survival – observed time), we allocated age-specific per month continuing/terminal phase costs and thereby estimated censoring-adjusted total health care cost for each patient. Cost data from 1992 to 2010 were adjusted for geographical location and inflation using price adjusters developed by Brown et al. [47]. Price adjusters were matched with patient's county at diagnosis using the registry code variable and Federal Information Processing Standard county code from the SEER data. Price adjusters allowed the conversion of costs to 2009 US dollars, and adjustment to 2013 US dollars was calculated using medical care consumer price index [48]. Costs were discounted at 3% per annum [49,50].

Cost-Effectiveness Analysis

ICERs were calculated for anthracycline-based chemotherapy versus no chemotherapy and non–anthracycline-based chemotherapy versus anthracycline-based chemotherapy using life-years and QALYs gained. As ICER is a ratio statistic, 95% confidence intervals were approximated from 5000 bootstrap samples. Cost-effectiveness acceptability curves were generated using the proportion of bootstrap sample ICERs that fell below a range of willingness-to-pay (WTP) thresholds. ICERs were calculated for best-case and worst-case scenarios and for different age groups. A secondary analysis calculated ICERs on the basis of data from the entire sample of 14,610 patients (unmatched cohort) using the IPTW approach assuming log-normal distribution for survival time [34,51].

Results

The 1:1:1 nearest-neighbor–matched sample included a total of 4575 patients, with 1525 patients in each treatment group (Table 2). Chi-square tests and standardized difference indicate that the three treatment groups were well balanced for patient and tumor characteristics (tumor stage, tumor size, node positive/negative, and tumor grade), geographic areas, and year of diagnosis. Appendix Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.08.008 presents total phase-specific health care costs per month for each treatment group. Overall, the highest per month cost was observed in the terminal phase (range $5140–$6554), followed by the initial phase (range $2499–$4539) and then the continuing phase (range $985–$1336). Costs for the anthracycline-based chemotherapy group were the highest during the initial ($4539) and terminal ($6554) phase, whereas costs were highest for non–anthracycline-based chemotherapy group during the continuing phase ($1336).

Table 2 – Distribution of characteristics by chemotherapy status in patients with breast cancer.

Characteristic (total N = 4575)	n (%)			P value	Standardized difference
	No chemotherapy (N = 1525)	Non– anthracycline-based chemotherapy (N = 1525)	Anthracycline-based chemotherapy (N = 1525)		
Age (y)				0.480	0.07
65–69	568 (37.3)	558 (36.6)	578 (37.9)		
70–74	501 (32.9)	513 (33.6)	487 (31.9)		
75–79	362 (23.7)	335 (22.0)	344 (22.6)		
80+	94 (6.2)	119 (7.8)	116 (7.6)		
Race/ethnicity				0.376	0.03
White	1254 (82.273)	1272 (83.4)	1252 (82.1)		
Black	184 (12.1)	171 (11.2)	168 (11.0)		
Other	87 (5.7)	82 (5.4)	105 (6.9)		
Marital status				0.916	0.03
Married	750 (49.2)	774 (50.8)	759 (49.8)		
Unmarried	732 (48.0)	706 (46.3)	720 (47.2)		
Unknown	43 (2.8)	45 (3.0)	46 (3.0)		
Tumor AJCC stage				0.937	0.02
Stage I	603 (39.5)	593 (38.9)	582 (38.2)		
Stage II	809 (53.1)	812 (53.3)	822 (53.9)		
Stage III	113 (7.4)	120 (7.9)	121 (7.9)		
Tumor size (cm)				0.745	0.07
<1.0	119 (7.8)	134 (8.8)	122 (8.0)		
1.0–<2.0	559 (36.66)	537 (35.21)	542 (35.5)		
2.0–<4.0	619 (40.59)	599 (39.28)	618 (40.5)		
4+/unknown*	228 (15.0)	255 (16.7)	243 (15.9)		
Node positive/negative				0.532	0.06
Positive	460 (30.2)	489 (32.1)	480 (31.5)		
Negative	995 (65.3)	953 (62.5)	964 (63.2)		
Unknown	70 (4.6)	83 (5.4)	81 (5.3)		
Tumor grade				0.546	0.05
Well/moderately differentiated	377 (24.7)	372 (24.4)	385 (25.3)		
Poorly/ undifferentiated	1,066 (69.9)	1086 (71.2)	1055 (69.2)		
Unknown/missing	82 (5.4)	67 (4.4)	85 (5.6)		
Surgery				0.914	−0.01
Breast-conserving surgery	747 (49.0)	738 (48.4)	736 (48.3)		
Mastectomy	778 (51.0)	787 (51.6)	789 (51.7)		
Radiation				0.840	−0.01
Yes	913 (59.9)	904 (59.3)	897 (58.8)		
No	612 (40.1)	621 (40.7)	628 (41.2)		
Comorbidity scores				0.851	0.03
0	1,018 (66.8)	1,036 (67.9)	1,034 (67.8)		
1	336 (22.0)	332 (21.8)	338 (22.2)		
≥2	171 (11.2)	157 (10.3)	153 (10.0)		
SES (poverty)				0.792	0.04
First (low SES)	413 (27.1)	430 (28.2)	440 (28.9)		
Second	365 (23.9)	366 (24.0)	382 (25.1)		
Third	383 (25.1)	362 (23.7)	358 (23.5)		
Fourth (high SES)	364 (23.9)	367 (24.1)	345 (22.6)		
SEER areas				0.537	0.06
Midwest	276 (18.1)	263 (17.3)	248 (16.3)		
Northeast	283 (18.6)	319 (20.9)	295 (19.3)		
South	299 (19.6)	305 (20.0)	316 (20.7)		
West	667 (43.7)	638 (41.8)	666 (43.7)		
Year of diagnosis				0.997	0.11
1992	23 (1.5)	20 (1.3)	27 (1.8)		
1993	29 (1.9)	23 (1.5)	23 (1.5)		
1994	15 (1.0)	22 (1.4)	22 (1.4)		

continued on next page

Table 2 – *continued*

Characteristic (total N = 4575)	n (%)			P value	Standardized difference
	No chemotherapy (N = 1525)	Non– anthracycline-based chemotherapy (N = 1525)	Anthracycline-based chemotherapy (N = 1525)		
1995	44 (2.9)	37 (2.4)	35 (2.3)		
1996	39 (2.6)	29 (1.9)	34 (2.2)		
1997	37 (2.4)	52 (3.4)	37 (2.4)		
1998	47 (3.1)	53 (3.5)	48 (3.2)		
1999	61 (4.0)	54 (3.5)	57 (3.7)		
2000	105 (6.9)	110 (7.2)	103 (6.8)		
2001	116 (7.6)	116 (7.6)	120 (7.9)		
2002	134 (8.8)	125 (8.2)	143 (9.4)		
2003	124 (8.1)	122 (8.0)	123 (8.1)		
2004	112 (7.3)	112 (7.3)	104 (6.8)		
2005	127 (8.3)	114 (7.5)	126 (8.3)		
2006	162 (10.6)	173 (11.3)	159 (10.4)		
2007	149 (9.8)	148 (9.7)	147 (9.6)		
2008	99 (6.5)	102 (6.7)	98 (6.4)		
2009	102 (6.7)	113 (7.4)	119 (7.8)		

AJCC, American Joint Committee on Cancer; SEER, Surveillance Epidemiology, End Results; SES, socioeconomic status.
* The small number of cases with unknown tumor size was combined with the tumor size 4+ category, which was reported because of the Data User Agreement rule that requires no number of cases in each cell <11.

Table 3 presents the total health care costs, effectiveness, and ICERs for the three treatment groups with mean values for costs and median effectiveness measures. Total health care costs were highest for the non–anthracycline-based chemotherapy group ($122,791) as compared with anthracycline-based chemotherapy group ($119,055) and no chemotherapy group ($86,383). Patients on anthracycline-based chemotherapy incurred less health care cost and gained more years of life than did patients on non–anthracycline-based chemotherapy. Median life-years for the anthracycline group were 10.97 and 9.58 for the non–anthracycline-based group compared with 8.37 for the no chemotherapy group. Median QALYs for the anthracycline-based group and the non–anthracycline-based group were 12.05 and 9.56, respectively, compared with 7.81 for the no chemotherapy group. The ICER for anthracycline-basd group (vs. the no chemotherapy group) was $12,566 per life-year gained and $7688 per QALY gained, respectively. The non–anthracycline-based group was dominated (more costly and less effective) compared with the anthracycline group. Results for best-case and worst-case scenarios were similar to results for the base-case analysis; ICERs per QALY gained were $7969 and $8783 for the best-case and worst-case scenario, respectively (data not shown). Results were similar to results of the base-case analysis using mean effectiveness and the IPTW approach (data not shown).

All bootstrap samples comparing anthracycline-based chemotherapy versus no chemotherapy were in the northeast quadrant (more costly and more effective) of the cost-effectiveness plane (data not shown). Cost-effectiveness acceptability curves demonstrate that anthracycline-based chemotherapy was nearly 100% cost-effective at a WTP threshold of $50,000 as compared with no chemotherapy Fig. 1.

Table 4 presents the effectiveness and cost-effectiveness of chemotherapy treatments stratified by age, and Appendix Table 6 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.08.008 presents the patient and tumor characteristics by age. Overall, as age increases, the effectiveness of chemotherapy decreased (Fig. 2). The median QALYs for anthracycline-based chemotherapy for the 65 to 69 years age group was 21.91 QALYs

Table 3 – Effectiveness and cost-effectiveness for chemotherapy treatment groups*.

Chemotherapy treatment group	Effectiveness		Total Health care cost† ($) Mean (SE)	ICER ($)	
	Median life-years (95% CI)	Median QALY (95% CI)		Per median life-year gained (95% CI)	Per median QALY gained (95% CI)
No chemotherapy	8.37 (7.79–9.10)	7.81 (7.19–8.63)	86,383 (2157.09)	–	–
Anthracycline-based	10.97 (9.51–14.01)	12.05 (9.92– NA)	119,055 (2327.32)	12,566 (5,617–36,599)	7,688 (5,398–18,429)
Non–anthracycline-based	9.58 (9.05–10.43)	9.56 (8.19–10.57)	122,791 (2894.94)	Dominated	Dominated

CI, confidence interval; ICER, incremental cost-effectiveness ratio; NA, not available; QALY, quality-adjusted life-year; SE, standard error.
* Treatment groups arranged in ascending order of cost.
† 2013 US dollars.

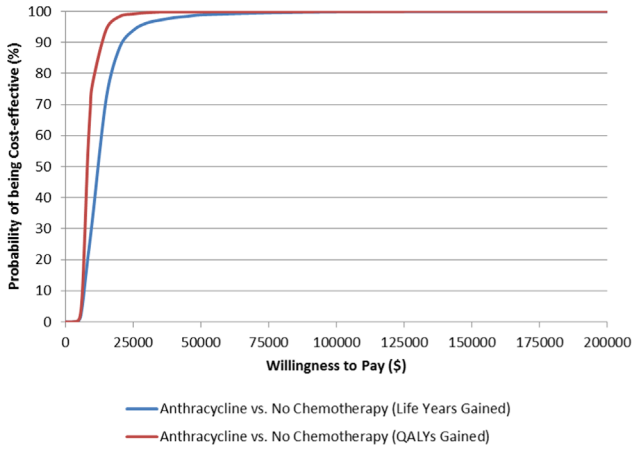

Fig. 1 – Cost-effectiveness acceptability curve—All age groups. QALY, quality-adjusted life-year. (Color version of figure available online).

versus 4.79 QALYs for the 80+ years age group. Compared with no chemotherapy, anthracycline-based chemotherapy had an ICER of $6691 per life-year gained and $3790 per QALY gained for the 65 to 69 years age group; $12,500 per life-year gained and $10,801 per QALY gained for the 70 to 74 years age group; and $94,538 per life-year gained and $90,405 per QALY gained for the 80+ years age group. In the 75 to 79 years age group, the ICER for non–anthracycline-based chemotherapy versus no chemotherapy was $14,137 per life-year gained and $10,259 per QALY gained and anthracycline-based chemotherapy was dominated when quality of life was considered. Censoring-adjusted total health care costs did not change the basic cost-effectiveness conclusions. The ICER estimates increased but were within the commonly referenced benchmark of $100,000/QALY, except for the 80+ years age group in which the ICER/QALY was marginally over the benchmark (data not shown).

Discussion

This study examined the effectiveness and cost-effectiveness of chemotherapy for older women with breast cancer stratified by age within a large community cohort of patients treated from 1992 to 2009 in the United States. The results largely confirmed the findings from a previous, more restrictive randomized clinical trial that reported that overall treatment effectiveness declined with age and anthracycline-based chemotherapy was cost-effective relative to non–anthracycline-based chemotherapy and no chemotherapy [5].

Age group–specific results show that anthracycline regimens were most cost-effective for people aged 65 to 69, 70 to 74, and 80+ years, but non–anthracycline-based regimens were most cost-effective for people aged 75 to 79 years, especially when quality of life was considered. Comparing anthracycline to no chemotherapy for those aged 75 to 79 years, however, yielded an ICER of $19,647 per QALY gained, also well within the commonly cited WTP US threshold. Although remaining highly cost-effective, there was a trend for the ICERs to more than double between the 65 and 69 years and the 70 and 74 years age groups when comparing no chemotherapy to anthracycline-based therapy, with non–anthracycline-based therapy being dominated in each case.

The trend for the two oldest age groups was for the anthracycline ICER to approach the $100,000 benchmark while dominating the non–anthracycline-based therapy in the 80+ years age group. The oldest age groups benefit from treatment, but gains in life-years and QALYs are less than for younger groups. These outcome trends with age differ from previous studies that incorporated few patients beyond the age of 70 years [14]. Our ICER trends with age are consistent with a previous modeling study with parameters based on a systematic literature review [5].

Table 4 – Effectiveness and cost-effectiveness for chemotherapy treatment groups*.

Chemotherapy treatment group	Effectiveness		Total health care cost† ($) Mean (SE)	ICER ($)	
	Median life-years (95% CI)	Median QALY (95% CI)		Per median life-year gained	Per median QALY gained
65–69 y					
No chemotherapy	11.21 (9.26–13.58)	13.71 (10.25–18.35)	81,261 (3533.83)	–	–
Anthracycline-based	15.86 (12.75–19.73)	21.91 (15.71–30.57)	112,358 (3866.88)	6,691	3,790
Non–anthracycline-based	13.85 (11.25–17.06)	17.99 (13.14–24.63)	122,631 (4774.74)	Dominated	Dominated
70–74 y					
No chemotherapy	8.85 (7.70–10.09)	7.97 (6.75–10.24)	90,617 (3964.34)	–	–
Anthracycline-based	10.97 (8.99–14.01)	10.42 (8.94–NA)	117,141 (3896.55)	12,500	10,801
Non–anthracycline-based	9.11 (8.64–11.36)	8.70 (7.51–12.23)	127,956 (5860.94)	Dominated	Dominated
75–79 y					
No chemotherapy	6.07 (5.24–7.14)	5.17 (4.28–6.45)	89,210 (3996.89)	–	–
Non–anthracycline-based	8.00 (5.78–9.58)	7.81 (5.46–10.03)	116,385 (4862.09)	14,137	10,259
Anthracycline-based	8.15 (6.95–9.51)	7.18 (6.48–NA)	128,701 (5275.21)	76,213	Dominated
80+ y					
No chemotherapy	5.12 (3.62–6.46)	4.26 (2.64–5.53)	83,875 (9203.27)	–	–
Non–anthracycline-based	4.47 (3.40–5.86)	3.50 (2.31–4.72)	119,304 (7037.37)	Dominated	Dominated
Anthracycline-based	5.63 (4.23–7.64)	4.79 (3.31–6.75)	131,853 (6957.07)	94,538	90,405

CI, confidence interval; ICER, incremental cost-effectiveness ratio; NA, not available; QALY, quality-adjusted life- year; SE, standard error.
* Treatment groups arranged in ascending order of cost.
† 2013 US dollars.

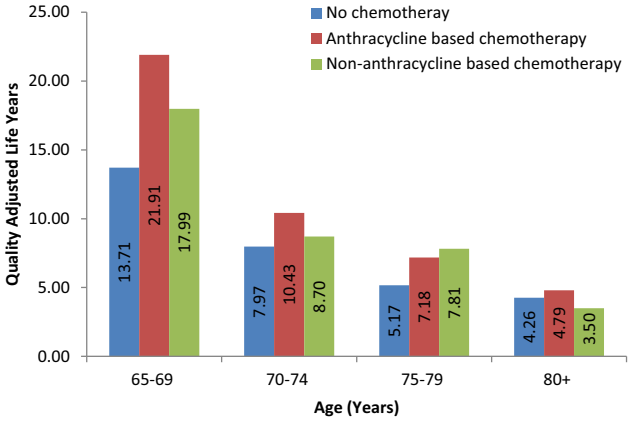

Fig. 2 – Effectiveness of treatment groups by age categories. (Color version of figure available online).

Our aberrant ICER results comparing anthracycline-based to non–anthracycline-based chemotherapy for the 75 to 79 years age group may be because of the higher disease stage at diagnosis in the older age groups and statistical variability in the data. About 75% of the cases were diagnosed at stage II/III in the 75 to 79 years age group compared with 50% to 60% in the younger age groups. On comparing anthracycline-based and non–anthracycline-based groups, the probability of being cost-effective reaches only about 50% at a WTP of $200,000 per life-year gained. In all other comparisons, the probability of treatments being cost-effective for the 75 to 79 years age group and younger groups reach 90% or 95% at the $50,000 WTP threshold. There was therefore no compelling economic evidence to favor non–anthracycline-based chemotherapy for the 75 to 79 years age group. Both treatments were very cost-effective compared with no chemotherapy.

A meta-analysis of 123 clinical trials found that long-term outcomes of anthracycline- based chemotherapy compared with no chemotherapy was unrelated to age up to age 70 years. In contrast, the efficacy of cyclophosphamide, methotrexate, and fluorouracil compared with no chemotherapy was inversely related to age [14]. Results beyond age 70 years were not clear because of the limited number of cases. Our results show an inverse relationship between age and both median life-years and QALYs gained. For example, Appendix Table 4 found at http://dx.doi.org/10.1016/j.jval.2015.08.008 presents a median years of life gained of 4.65 for the 65 to 69 years age group, 2.12 for the 70 to 74 years age group, 2.08 for the 75 to 79 years age group, and 0.51 for the 80+ years age group. In addition to the limits imposed by the length of life, one possible explanation for these findings was that a lower dose of chemotherapy may be more commonly administered to elderly patients and/or there may be a lack of sensitivity to chemotherapy in elderly patients with breast cancer. We also found that the Kaplan-Meier–derived QALYs in the anthracycline group were higher than the life-years although they were not statistically different as confidence intervals overlap. A plausible reason for this finding was that quality-of-life adjustments were not significant (0.84–0.99 in the continuing phase), and so the differences between life-years and QALYs were minimal. When life-years were compared to the worst-case scenario (highest quality-of-life adjustment), however, median QALYs were lower than life-years but statistically insignificant.

Several studies have examined the economics associated with the treatment of early stage breast cancer [4,6,50], but few have 1) included a "no chemotherapy" group, 2) compared anthracycline-based versus non–anthracycline-based regimens, and 3) examined results stratified by age group for older women, including women beyond the age of 70 years.

More recent studies have focused on comparisons of anthracycline regimens with the addition of targeted therapies [52,53]. Campbell et al. [5] published a study with research questions similar to ours, although it was based on a Markov model to simulate the natural history of early breast cancer and the impact of alternative chemotherapy regimens. The model used parameters from randomized clinical trials conducted in the United Kingdom [54–56] and a systematic literature review [13]. They compared no chemotherapy with a first-generation regimen (i.e., non–anthracycline-based) with second-generation (anthracycline-based regimen) and third-generation regimens (anthracycline + taxane–based regimen). Costs were estimated from studies in the United Kingdom [57,58].

For older women, the third-generation treatment was most cost-effective if they were estrogen receptor–positive and had a 10-year recurrence rate of less than 53% to 54%. Between the 53% to 54% and 80% range, the second-generation therapy was the cost-effective treatment, and above that level of risk, no chemotherapy was optimal. Our study found similar results, although the patients in the current study ranged from 65 to 80+ years. Anthracycline (second- and third-generation therapies) dominated non–anthracycline-based (first-generation therapies) chemotherapy, and both were found to be cost-effective relative to no chemotherapy. Of note is that the ICERs were well below the commonly cited US WTP thresholds of $50,000 to $100,000 per QALY for 65 to 69 and 70 to 74 years age groups. Non–anthracycline-based chemotherapy was dominated in the 80+ years age group and the ICER for anthracycline-based compared with no chemotherapy was near the high end of the common US WTP range.

Markov models were developed on the basis of evidence from the literature and the Breast Cancer International Research Group trial to evaluate the cost-effectiveness of TAC (docetaxel, doxorubicin, and cyclophosphamide) compared with FAC (fluorouracil, doxorubicin, and cyclophosphamide) in the treatment of early node-positive breast cancer from the Canadian [4] and UK [50] perspectives. In both cases, TAC was found to be cost-effective compared with FAC by standard conservative WTP thresholds. The UK study examined subgroups by age and found an incremental cost per QALY of £13,718 for women younger than 50 years compared with £25,826 for women 50 years or older.

Our study has several limitations that should be considered for interpretation of the findings. The primary concern was the effects of selection bias and confounding by indication on the study findings because patients were not randomly assigned into one of the three chemotherapy groups. For example, age and comorbidity may affect patient choice in regard to whether and how much chemotherapy to undergo [59]. Age and comorbidity are both available in the data and were used to construct the propensity score–matched groups. We also stratified the analysis by age group. Despite the use of 1:1:1 propensity score matching, unmeasured or unknown factors may differ in ways that affect patient outcomes in each of the comparison groups. In addition, the use of propensity score matching approach reduces the sample size, which may result in a selective population and not represent the population. A more robust method of addressing selection bias such as instrumental variable analysis may be appropriate; however, finding a valid instrument is challenging using observational data sets such as SEER-Medicare [60,61].

Our primary analysis combined stages I, II, and IIIa, which may mask cost-effectiveness for the individual stages. A secondary analysis in Appendix Table 4 shows results for stages II and IIIa. We were unable to estimate median survival for all chemotherapy regimens for stage I because survival probability did not reach 0.5. We found that the non–anthracycline-based group was dominated in both stage II and IIIa and ICER per QALY for stage II was $13,060 and for stage IIIa was $178,120 for anthracycline-based chemotherapy versus no chemotherapy. These results are

in line with our age-specific results because most of the patients in the 70 to 74 and 75 to 79 years age groups are in stage II (Appendix Table 6) and in the 80+ years age group there are relatively more patients in stage IIIa.

Cases from the SEER-Medicare data were not representative of all cancer cases in the United States. The study also excluded members of health maintenance organizations during the study period, limiting its generalizability to those patients, but treatment costs and survival may not differ between health maintenance organizations and other managed preferred provider organization models of care that rely on fee-for-service payment [62]. Because of smaller numbers, the subgroup analyses based on age group should be considered cautiously, particularly for those patients in the 80+ years age group. The results of the study should also be interpreted in light of considerable changes that occurred in breast cancer care over the period 1992 to 2009. For example, docetaxel and trastuzumab were approved in 2004 and 2006, respectively, as adjuvant therapy for node-positive patients with early breast cancer, which may have substantially increased patients' total cost. Trastuzumab was administered in 15.5% of non–anthracycline-based group patients and in 9.3% of anthracycline-based group patients, which may explain the marginally higher total health care cost for the non–anthracycline-based group. Finally, costs were measured from a payer perspective on the basis of amounts Medicare paid for the services. It was likely that societal costs, which include indirect costs, may not be much different, given the retirement age of the study population.

Conclusion

In conclusion, anthracycline-based chemotherapy was cost-effective for treating early stage (stage I, II, or IIIa) breast cancer among older patients when compared with non–anthracycline-based chemotherapy and no chemotherapy. The cost per QALY gained for anthracycline-based chemotherapy fell within conservative WTP thresholds of less than $100,000 for most age groups. Age group–specific analysis confirmed these results, except for the 75 to 79 years age group.

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Supplemental Material

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