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Simulation of Chemotherapy Effects in Older Breast Cancer Patients With High Recurrence Scores

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Abstract

Background: Tumor genomic expression profile data are used to guide chemotherapy choice, but there are gaps in evidence for women aged 65 years and older. We estimate chemotherapy effects by age and comorbidity level among women with early-stage, hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancers and Oncotype DX scores of 26 or higher.
Methods: A discrete-time stochastic state transition simulation model synthesized data from population studies and clinical trials to estimate outcomes over a 25-year horizon for subgroups based on age (65–69, 70–74, 75–79, and 80–89 years) and comorbidity levels (no or low, moderate, severe). Outcomes were discounted at 3%, and included quality-adjusted life-years (QALYs), life-years, and breast cancer and other-cause mortality with chemoendocrine vs endocrine therapy. Sensitivity analysis tested the effect of varying uncertain parameters.
Results: Women aged 65–69 years with no or low comorbidity gained 0.16 QALYs with chemo-endocrine and reduced breast cancer mortality from 34.8% to 29.7%, for an absolute difference of 5.1%; this benefit was associated with a 12.8% rate of grade 3–4 toxicity. Women aged 65–69 years with no or low or moderate comorbidity levels, and women aged 70–74 years with no or low comorbidity had small chemotherapy benefits. All women aged 75 years and older experienced net losses in QALYs with chemo-endocrine therapy. The results were robust in sensitivity analyses. Chemotherapy had greater benefits as treatment effectiveness increased, but toxicity reduced the QALYs gained.
Conclusion: Among women aged 65–89 years whose tumors indicate a high recurrence risk, only those aged 65–74 years with no or low or moderate comorbidity have small benefits from adding chemotherapy to endocrine therapy. Genomic expression profile testing (and chemotherapy use) should be reserved for women aged younger than 75 years without severe comorbidity.

Tumor genomic profile data increasingly are used to guide the adjuvant chemotherapy choices for treatment of early-stage breast cancer (1,2). However, there are gaps in evidence about how to best make treatment decisions based on genomic information for women aged 65 years and older ("older"), despite this group comprising the majority of women diagnosed each year in the United States with early-stage, hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative cancers (3).

There are several reasons for these gaps. First, the net balance of benefits and harms of chemotherapy in older women is likely to differ from that in younger women because of differences in age-specific distributions of competing risks related to treatment toxicity, distant recurrence, or mortality from comorbid illnesses (4). There is also heterogeneity in health within the older population that influences treatment tolerance and benefits (5).Geriatric assessment is being increasingly used in practice to assess health in older patients (6,7) and to predict the

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risk of chemotherapy toxicity and mortality(8,9). Elements of geriatric assessment are also used in tools like ePrognosis to estimate life expectancy and guide treatment decisions (10–13). However, none of these tools considers genomic risk in systemic treatment recommendations for older women.

Other reasons for evidence gaps in integrating genomic information into care of older women include low testing rates (14), underrepresentation of older women in trials examining use of tumor genomic profile testing (2), and lack of genomic test data in the few trials specific to older women (15).

To fill gaps in evidence about systemic therapy decisions for older women, we used simulation modeling to estimate benefits and harms of chemoendocrine vs endocrine therapy by age and comorbidity level among older women with early-stage, estrogen receptor (ER)–positive, HER2-negative breast cancers with Oncotype DX recurrence risk scores (RSs) of 26 or greater. The results are intended for use in concert with geriatric assessment to support care and guidelines for older breast cancer patients.

Methods

We simulated the population of older women with early-stage breast cancers and varying levels of comorbidity. The Georgetown University Oncology Institutional Review Board approved this research as exempt based on use of deidentified publicly available data.

Population and Intervention

The population modeled included women aged 65–89 years and diagnosed with stage I or IIA, node-negative, ER-positive, HER2-negative breast cancer and an Oncotype DX RS of 26 or greater. We focused on this group because the Trial Assigning Individualized Options for Treatment (TAILORx) included chemotherapy in those with an Oncotype DX RS of 26 or greater, based on higher risk of recurrence (1). We modeled Oncotype DX because it is the most commonly used gene expression profiling (GEP) test in the United States (14,16).

Simulated women had varying levels of comorbidity, based on population prevalence (17). Because there are no large, nationally representative geriatric datasets, we used comorbidity as a proxy for key elements of the geriatric assessment because there are good national data on comorbid conditions among breast cancer patients (ie, Surveillance, Epidemiology, and End Results [SEER]-Medicare data) (18). The conditions included in each comorbidity level have been published elsewhere (17,18).

Approximately 15% of older women diagnosed with ER+/HER2– stage I and II cancers are expected to have an Oncotype DX score of 26 or greater (16,19). We assumed these women received hormonal therapy (eg, tamoxifen or aromatase inhibitor) and evaluated outcomes with and without use of chemotherapy.

Model Overview

A discrete-time stochastic state transition model was used to depict the life history of each woman with breast cancer from diagnosis to death (or 25 years), given her comorbidity-specific life expectancy. A detailed model description has been published elsewhere (20). A 25-year time horizon was chosen because it includes the life expectancy of nearly all older women and is long enough to capture expected distant recurrences (21,22). The model simulated women in combinations of age groups (65–69, 70–74, 75–79, and 80–89 years), and comorbidity level (none, low, moderate, and severe). Five million runs were conducted for each group. The model was programmed using TreeAge Pro 2015 (TreeAge Software, Williamstown, MA).

Input Parameters

Model input parameters (Table 1) were derived from national population data, trial results, and other published studies. Incidence rates were based on 2008–2014 SEER data. We applied the Bayes theorem to data from the TAILORx trial to calculate the probability of RS of 26 or greater, conditional on whether recurrence occurred (1). Survival in the absence of treatment for ER+/HER2– cancers was based on prior analyses of the Cancer Intervention and Surveillance Modeling Network (CISNET) Breast Cancer Working group (23). We modeled anthracyclines and aromatase inhibitors; alternative regimens (ie, cyclophosphamide, methotrexate, and fluorouracil [CMF] or combination anthracycline and taxane regimens) were tested in sensitivity analyses. Treatment efficacy was based on meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (30) and was implemented by reducing the hazard of breast cancer death among women with distant recurrence. For those without distant recurrence, there was no benefit of chemotherapy, but they might experience chemotherapy toxicity.

We used comorbidity-specific noncancer survival data derived by Mariotto and colleagues from a random 5% sample of women enrolled in the Medicare Part A and B program in SEER areas (17,18). Based on mortality associated with 16 comorbid conditions, women were grouped into four comorbidity levels: no, low, moderate, and severe. Because only 2% were in the low category, we used a weighted average of the mortality in the no- and low-comorbidity group. The age-specific rates of chemotherapy toxicity by grade (3–4 vs 5) were derived from published trials and Medicare data (15,24–27,37), and were adjusted for comorbidity to derive comorbidity-specific probabilities of toxicity (28,38).

Utility values began with the national female population age-specific values for general health from the EQ-5D reported on the Medical Expenditure Panel Survey (31,32). Utilities were then adjusted for cancer (stages I and II), chemotherapy use and toxicity, and distant recurrence (33–36). Because all women received endocrine therapy, we did not include specific disutility for this treatment modality.

Analyses

The primary outcome was 3% discounted quality-adjusted life-years (QALYs) for each treatment strategy (chemoendocrine and endocrine therapy). QALYs were obtained from sum of life-year(s) multiplied by the utility value of each event within the corresponding state period. We also included discounted and undiscounted life-years of survival, breast cancer mortality, other-cause mortality, and grade 3–4 and 5 chemotherapy toxicity. Each outcome was calculated for the 12 subgroups of women for each treatment strategy based on combinations of four age groups (65–69, 70–74, 75–79, and 80–89 years) and three comorbidity levels (no or low, moderate, and severe).

The incremental differences in outcomes with chemoendocrine vs endocrine therapy were calculated for each group. Positive incremental QALYs indicated that

Table 1. Model input parameters for estimation of outcomes among older women with ER-positive, HER2-negative, lymph node–negative breast cancers*

Parameter	Value/range/description	Source
Age- and comorbidity-specific life tables	SEER-Medicare data in 1992–2005	Lansdorp-Vogelaar, et al. 2014 (17) Mariotto, et al. 2013 (17,18)
Age- and stage-specific distribution of ER-positive, HER2-negative breast cancers*	Women aged 65 y and older, diagnosed with ER-positive breast cancer, 2008–2014	SEER 2017 (3)
Probability of distant recurrence among ER-positive, HER2-negative patients in the absence of treatment, conditional on stage and age		Munoz and Plevritis 2018 (23)
Stage I, y		(23)
Age 65–69	0.238	
Age 70 and older	0.236	
Stage II (node neg), y		
Age 65–69	0.378	
Age 70 and older	0.370	
Oncotype DX test results conditional on recurrence or nonrecurrence		Sparano, et al. 2018 (1) Paik, et al. 2004 (2)
Pr (score category | recur) (95% CI)		(1,2)
26+	0.742 (0.773–0.719)	
Pr (score category | not recur) (95% CI)		
26 or greater	0.17 (0.174–0.166)	
Rates of chemotherapy toxicity by grade and comorbidity level		Muss, et al. 2009 (15) Muss, et al. 2007 (24) Caparica, et al. 2019 (25) Reinisch, et al. 2013 (26) Enright, et al. 2015 (27) Edwards, et al. 2017 (28)
Grade 3, 4 toxicity		(15,24–28)
No or low	0.128 (0.089–0.167)	
Moderate	0.172 (0.150–0.197)	
Severe	0.246 (0.176–0.332)	
Grade 5 toxicity		
No or low	0.012 (0.002–0.025)	
Moderate	0.018 (0.015–0.029)	
Severe	0.027 (0.018–0.041)	
Breast cancer–specific survival rate by age and stage in the absence of systemic therapy		Munoz and Plevritis 2018 (23) Plevritis, et al. 2018 (29)
No recurrence	Infinite (cured)	(23,29)
Recurrence	25-year breast cancer survival before adjuvant treatment by joint ER-positive, HER2 status; age group; and American Joint Committee on Cancer stage	
Reduction in hazard of death with adjuvant therapy	Changes the survival function in absence of treatment for those destined to have distant recurrence; all women are assumed to receive hormonal therapy	EBCTCG 2012 (30) Plevritis, et al. 2018 (29) (29,30)
Base age-specific utility (and range) for US women		Hanmer, et al. 2006 (31) AHRQ 2017 (32)
Age, healthy base value (range), y		(31,32)
60–65	0.811 (0.800–0.822)	
70–75	0.771 (0.758–0.784)	
80–85	0.724 (0.701–0.747)	
Utilities for cancer-related states (reduction in quality of life)		Shih, et al. 2012 (33) Tan, et al. 2014 (34) Wouters, et al. 2013 (35) Sorensen, et al. 2004 (36)
Stage I	0.9	(33–36)
Stage IIA	0.85	
Chemotherapy	0.9 (6-mo duration)	
Grade 3–4 toxicity	0.7 (6-mo duration)	
Distant recurrence	0.4 (≤ 3 y)	

*AHRQ = Agency for Healthcare Research and Quality; CI = confidence interval; EBCTCG = Early Breast Cancer Trialists' Collaborative Group; ER = estrogen-receptor; HER2 = human epidermal growth factor receptor 2; SEER = Surveillance, Epidemiology, and End Results.

chemotherapy benefits outweighed its harms; negative values indicated that toxicity harms were greater than benefits.

SAS 9.4 (SAS Institute, Cary, NC) was used for postsimulation calculation of outcomes, including application of discounting and utility weights.

Sensitivity Analyses

Sensitivity analyses were used to examine the effect of varying the estimated values of input parameters on model outcomes. First, probability of chemotherapy toxicity was varied across the 95% confidence interval (CI). Second, to examine impact of Oncotype DX RS's predictive performance on outcomes, we varied the probability of having a recurrence score of 26 or greater, given occurrence or nonoccurrence of distant recurrence across the upper and lower limits of the 95% confidence interval of the base parameter (2). Third, we varied chemotherapy regimens (more or less effective than anthracycline-based regimens) to test the effect of treatment effectiveness (and their respective toxicity rates) on conclusions about use of chemotherapy. Finally, to capture the effect of time preferences on outcomes, QALYs were also discounted at alternative rates of 1% and 5% per year.

Model Validation

We assessed model validity in several manners. First, internal validity was verified by examining whether the model output varied in the expected directions when using extreme values of parameters. Second, face validity was evaluated by review of the fidelity of the model and model assumptions to clinical practice. Third, predictive validity was evaluated by comparing age-specific breast cancer mortality in the United States for women aged 65 years or older with stage I and II, ER-positive, HER2-negative breast cancers, and known Oncotype DX scores of 26 or greater from the linked SEER-Genomic Health Inc dataset with model projected mortality rates derived by weighting the age- and comorbidity-level groups based on their prevalence in the population, and assuming observed population chemotherapy patterns (16,29).

Results

Breast Cancer Mortality Rate and Distant Recurrence Rate

The model closely projected observed US age-specific breast cancer mortality rates among older women with early-stage, ER-positive, HER2-negative cancers and Oncotype DX scores of 26 or greater (Supplementary Figure 1, available online). In the absence of any adjuvant therapy, distant recurrence would be expected in 23.8%–23.6% (stage I) to 37.8%–37.0% (stage II) of these older women over a 25-year time horizon (Table 1).

Chemoendocrine vs Endocrine Therapy Effects by Comorbidity

Among older women with Oncotype DX scores of 26 or greater, there were small average gains in discounted QALYs with use of chemoendocrine vs endocrine therapy for those aged 65–69 and 70–74 years with no or low or moderate comorbidity (0.16–0.07 QALY and 0.08–0.04 QALYs, respectively). The magnitude of the gains decreased as comorbidity level and age increased (Table 2 and Figure 1). These average results reflect no benefit for women who never recur, and 0.34–0.13 QALYs gained among women who have distant recurrence are more substantial. Effects of chemoendocrine vs endocrine therapy on undiscounted life-years saved are shown in Table 2.

There was no gain in QALYs for women aged 75 or older in any comorbidity group with chemoendocrine vs endocrine therapy. Grade 3–4 toxicity rates ranged from 12.8% in the youngest age, lowest comorbidity-level group to 24.5% in the oldest age, severe comorbidity group.

Cause of Death

Older women were more likely to die of other causes than breast cancer (Table 3). With addition of chemotherapy to endocrine therapy, breast cancer mortality among women aged 65–69 years and no or low comorbidity was reduced from 34.8% to 29.7%, for an absolute difference of 5.1%; reductions decreased with increasing age and comorbidity level (Table 3). Rates of grade 5 toxicity were low, ranging from 1.3% among women aged 65–69 years with no or low comorbidity, to 2.7% among women aged 80–89 years with severe comorbidity.

Sensitivity Analysis

As compared with a 3% discount rate, higher or lower discount rates essentially did not change conclusions about chemotherapy benefits (Supplementary Table 1, available online). The conclusions were essentially unchanged when varying chemotherapy toxicity rates (Supplementary Table 2, available online) or the predictive performance of Oncotype DX test (not shown). Use of more effective chemotherapy regimens increased toxicity but still improved survival (compared with the use of doxorubicin hydrochloride and cyclophosphamide) for net gains in QALYs, whereas lower effectiveness would diminish benefits (Supplementary Table 3, available online).

Discussion

This modeling study integrates data from GEP testing, including benefits and harms of chemotherapy, and age- and comorbidity-specific life expectancy, to guide chemotherapy decisions among older women with early-stage, ER-positive, HER2-negative breast cancers. The results suggest that among older women whose early-stage, ER-positive, HER2-negative breast cancers have an Oncotype DX recurrence score of 26 or higher, those aged 65–74 years with no or low to moderate comorbidity, or those aged 70–74 years with no or low comorbidity will benefit from adding chemotherapy to endocrine therapy regimens. The magnitude of average benefits on QALYs was small. Whereas older women primarily die of other causes, up to one-third of the youngest and healthiest older women will die of their breast cancers with endocrine therapy alone, and chemotherapy can modestly reduce this probability. Finally, there were no benefits to chemotherapy among women aged 75 years and older, regardless of comorbidity.

Older women represent 50% of new cases each year, but older women (39), especially those with comorbid illness, have historically been underrepresented in clinical trials relative to their proportions in the population (15,40). For example, 30% of the participants in the TAILORx were aged 61–75 years, but only 3%–5% of women were aged 71–75 years, and there were no

Table 2. Effects of chemoendocrine (vs endocrine) therapy on discounted quality-adjusted life-years and undiscounted life-years saved in older women with stage I and II, node-negative, ER-positive, HER2-negative breast cancers with Oncotype DX recurrence scores of 26 or greater by age group and comorbidity level over a 25-year simulation period

	No or low comorbidity level, Age, y				Moderate comorbidity level, Age, y				Severe comorbidity level, Age, y			
Life years	65–69	70–74	75–79	80–89	65–69	70–74	75–79	80–89	65–69	70–74	75–79	80–89
3% discounted quality-adjusted life-years												
Chemo+endocrine	7.17	4.72	2.53	0.8	6.18	3.94	2.32	0.8	5.26	3.56	2.31	0.78
Endocrine	7.01	4.65	2.56	0.83	6.1	3.9	2.35	0.83	5.26	3.61	2.36	0.83
Net benefit (loss)*	0.16	0.07	−0.03	−0.03	0.08	0.04	−0.03	−0.03	0	−0.05	−0.05	−0.05
Undiscounted life-years												
Chemo+endocrine	14.77	9.53	5.16	1.81	12.61	7.94	4.73	1.8	10.7	7.18	4.72	1.78
Endocrine	14.32	9.28	5.13	1.82	12.31	7.77	4.71	1.82	10.55	7.17	4.72	1.82
Net benefit (loss)*	0.45	0.25	0.03	−0.01	0.3	0.17	0.02	−0.02	0.15	0.01	0	−0.04

*A positive number indicates a gain in QALYs. A negative number indicates that chemotherapy would cause a loss of QALYs. Chemo = chemotherapy; ER = estrogen-receptor; HER2 = human epidermal growth factor receptor 2; QALYs = quality-adjusted life-years.

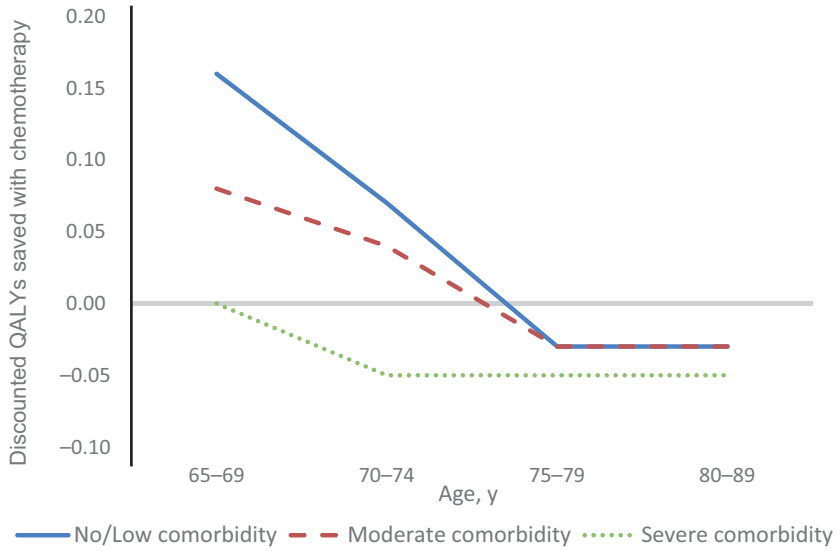

Figure 1. Discounted quality-adjusted life-years (QALYs) saved with chemotherapy in older women with stage I and II, node-negative, ER-positive, HER2-negative breast cancers with Oncotype DX recurrence scores of 26 or greater by age group and comorbidity level. Discounted QALYs saved with chemotherapy decreased with increasing age or comorbidity-level increased. Women aged 65–69 and 70–74 years with no or low or moderate comorbidity gained QALYs from chemoendocrine therapy (vs endocrine therapy). ER = estrogen-receptor; HER2 = human epidermal growth factor receptor 2.

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planned analyses for older women, and comorbidity data were not collected (1). Earlier trials specifically designed for older women did not have genomic profile data (15,24,30). Thus, clinicians are faced with a paucity of data to inform treatment discussions with older women.

Among older women with early-stage, ER-positive, HER2-negative breast cancer, only about 13–15% will have an RS of 26 or greater (16,19). Our model results indicate that benefits outweigh harms of chemotherapy among older women aged 65–74 years with early-stage, ER-positive, HER2-negative breast cancers with an RS of 26 or greater and no or low to moderate comorbidity. Additionally, because there were no benefits with chemotherapy, and even losses in QALYs in any comorbidity groups aged 75 years or older, our results suggest that Oncotype DX testing should be limited to older women younger than 75 years with no or low to moderate comorbidity levels. This adds to recent American Society of Clinical Oncology guidelines that are not comorbidity specific (6). Further, our results suggest that both age and comorbidity be included in future clinical decision tools integrating Oncotype DX and other clinical pathological data to translate trial results to use in treatment decision making with heterogeneous groups of older women.

The average magnitude of chemotherapy benefits was small even in older women with the least comorbidity. With small magnitude benefits, treatment toxicity becomes critical because a typical course of chemotherapy lasts for 1.5 months, and the decrements in quality of life may outweigh small gains in length of life. The gains in life with chemotherapy for women who actually recur are more substantial. However, although Oncotype DX scores are a useful marker of the probability of distant recurrence, most women with high recurrence RS do not actually recur (2). In this situation, individual preferences are important because older women most fear death from cancer, and for some older women, use of chemotherapy will reduce the probability of dying from breast cancer (41,42).

At present, it is not likely that there will be large, new trials of chemotherapy in older women with breast cancer that are powered to examine effects stratified by comorbidity level and

Table 3. Probability of death by age, cause, comorbidity, chemoendocrine (vs endocrine) therapy, and follow-up period in older women with stage I and II, node-negative, ER-positive, HER2-negative breast cancers with Oncotype DX recurrence scores of 26 or greater

	Age 65–69 y			Age 70–74 y			Age 75–79 y			Age 80–89 y		
Probability of death by follow-up, comorbidity, and treatment	Breast cancer death, %	Other-cause death, %	Toxicity death, %	Breast cancer death, %	Other-cause death, %	Toxicity death, %	Breast cancer death, %	Other-cause death, %	Toxicity death, %	Breast cancer death, %	Other-cause death, %	Toxicity death, %
25-year follow-up												
No or low comorbidity												
Chemo+endocrine	29.7	63.0	1.3	14.7	83.8	1.3	6.8	91.9	1.3	1.6	97.2	1.2
Endocrine	34.8	59.1	0.0	19.6	80.0	0.0	9.3	90.7	0.0	2.2	97.8	0.0
Net change*	−5.1	3.9	1.3	−5.0	3.8	1.3	−2.5	1.3	1.3	−0.7	−0.6	1.2
Moderate comorbidity												
Chemo+endocrine	24.2	69.6	1.8	11.8	86.2	1.7	6.0	92.2	1.7	1.6	96.7	1.8
Endocrine	28.9	66.5	0.0	15.9	83.8	0.0	8.9	91.1	0.0	2.2	97.8	0.0
Net change*	−4.7	3.1	1.8	−4.1	2.4	1.7	−2.9	1.1	1.7	−0.7	−1.1	1.8
Severe comorbidity												
Chemo+endocrine	20.0	73.8	2.7	10.7	86.5	2.7	6.1	91.1	2.8	1.5	95.7	2.7
Endocrine	24.2	72.2	0.0	14.5	85.3	0.0	8.6	91.4	0.0	2.3	97.8	0.0
Net change*	−4.2	1.6	2.7	−3.8	1.2	2.7	−2.5	−0.3	2.8	−0.7	−2.0	2.7
10-year follow-up												
No or low comorbidity												
Chemo+endocrine	13.4	14.0	1.3	10.6	48.3	1.3	6.3	83.2	1.3	1.6	97.1	1.2
Endocrine	18.0	13.8	0.0	14.9	47.8	0.0	8.7	82.5	0.0	2.2	97.6	0.0
Net change*	−4.6	0.3	1.3	−4.2	0.5	1.3	−2.4	0.7	1.3	−0.7	−0.6	1.2
Moderate comorbidity												
Chemo+endocrine	12.1	30.3	1.8	8.8	59.8	1.7	5.6	84.7	1.7	1.6	96.5	1.8
Endocrine	16.5	30.0	0.0	12.5	59.7	0.0	8.3	84.3	0.0	2.2	97.7	0.0
Net change*	−4.3	0.3	1.8	−3.7	0.1	1.7	−2.7	0.5	1.7	−0.7	−1.1	1.8
Severe comorbidity												
Chemo+endocrine	10.6	43.1	2.7	8.1	63.8	2.7	5.7	83.6	2.8	1.5	95.6	2.7
Endocrine	14.6	43.5	0.0	11.4	64.0	0.0	8.1	84.4	0.0	2.2	97.6	0.0
Net change*	−4.0	−0.4	2.7	−3.4	−0.2	2.7	−2.4	−0.8	2.8	−0.7	−2.0	2.7
5-year follow-up												
No or low comorbidity												
Chemo+endocrine	6.1	4.4	1.3	5.3	20.3	1.3	4.2	55.8	1.3	1.4	93.5	1.2
Endocrine	8.2	4.5	0.0	7.7	20.5	0.0	5.8	56.1	0.0	2.0	94.3	0.0
Net change*	−2.0	−0.1	1.3	−2.4	−0.2	1.3	−1.6	−0.3	1.3	−0.6	−0.7	1.2
Moderate comorbidity												
Chemo+endocrine	5.8	11.3	1.8	4.8	35.2	1.7	3.8	60.3	1.7	1.4	93.1	1.8
Endocrine	7.8	11.4	0.0	7.1	35.9	0.0	5.7	60.7	0.0	2.0	94.3	0.0
Net change*	−2.0	−0.1	1.8	−2.2	−0.8	1.7	−1.9	−0.4	1.7	−0.6	−1.2	1.8
Severe comorbidity												
Chemo+endocrine	5.4	22.2	2.7	4.5	41.5	2.7	3.8	59.1	2.8	1.4	92.2	2.7
Endocrine	7.3	22.6	0.0	6.6	42.1	0.0	5.6	60.6	0.0	2.1	94.3	0.0
Net change*	−1.9	−0.3	2.7	−2.0	−0.6	2.7	−1.9	−1.5	2.8	−0.7	−2.1	2.7

*Net change varies with outcomes. Negative value of net change in breast cancer death and positive value of net change in toxicity death came from use of chemotherapy. ER = estrogen-receptor; HER2 = human epidermal growth factor receptor 2.

GEP test results. In these situations, modeling can be useful by synthesizing the best available evidence and estimating outcomes for large populations of older women. By sampling a random combination of characteristics for each woman across the full distribution of possible joint distributions of these characteristics, modeling also provides robust estimates by capturing the uncertainty in each parameter.

We used modeling best practices, but there are several limitations that should be considered in evaluating our results. First, there were no large databases of older women with breast cancer that included life expectancy by function or other aspects of comorbidity relevant to daily function, so we used comorbidity-specific data from the SEER-Medicare database (17,18). It will be important to refine the model and capture greater heterogeneity in health and function as data evolve. Second, we assumed that hazard reductions with chemotherapy were similar in older and younger women (43–45), but dose reductions and incomplete cycles are more common in older patients, and could limit benefits. When we tested lower effectiveness rates, benefits diminished, so that our results might overestimate benefits, but this would not change the conclusion that there are only small benefits with chemotherapy in most older women with RSs of 26 or greater. Third, in estimating the predictive performance of Oncotype DX conditioned on recurrence, we used trial data from 9- to 10-year follow-up and assumed the same predictive performance over 25 years (22). Although we do not have data to test this assumption, results of sensitivity analysis for this parameter did not change conclusions. Finally, we considered decrements in quality of life based only on acute toxicity during active therapy. However, there are emerging data to suggest that some older women may experience persistent long-term adverse chemotherapy effects, including cardiotoxicity and cancer-related cognitive declines (42,46,47). These effects could reduce or eliminate the net benefits of chemotherapy in older women with favorable prognosis breast cancers.

In summary, our model results suggest that even with high-recurrence RS, women aged 65 years and older with severe comorbidity or aged 75 years and older with any comorbidity level do not benefit from chemotherapy, and even experience losses in QALYs because of toxicity; for these women, there is no indication for GEP testing. Integration of GEP test results with age and comorbidity may be useful to guide discussions with older women about the risks and benefits of chemotherapy.

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