Chemotherapy Was Not Associated With Cognitive Decline in Older Adults With Breast and Colorectal Cancer

Findings From a Prospective Cohort Study

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Objectives: This study tested 2 hypotheses: (1) chemotherapy increases the rate of cognitive decline in breast and colorectal cancer patients beyond what is typical of normal aging and (2) chemotherapy results in systematic cognitive declines when compared with breast and colorectal cancer patients who did not receive chemotherapy.

Subjects: Data came from personal interviews with a prospective cohort of patients with breast (n = 141) or colorectal cancer (n = 224) with incident disease drawn from the nationally representative Health and Retirement Study (1998–2006) with linked Medicare claims.

Measures: The 27-point modified Telephone Interview for Cognitive Status was used to assess cognitive functioning, focusing on memory and attention. We defined the smallest clinically significant change as 0.4 points per year.

Results: We used Bayesian hierarchical linear models to test the hypotheses, adjusting for multiple possible confounders. Eighty-eight patients were treated with chemotherapy; 277 were not. The mean age at diagnosis was 75.5. Patients were followed for a median of 3.1 years after diagnosis, with a range of 0 to 8.3 years. We found no differences in the rates of cognitive decline before and after diagnosis for patients who received chemotherapy in adjusted models ($P = 0.86$, one-sided 95% posterior intervals lower bound: 0.09 worse after chemotherapy), where patients served as their own controls. Moreover, the rate of cognitive decline after diagnosis did not differ between patients who had chemotherapy and those who did not ($P = 0.84$, one-sided 95% posterior intervals lower bound: 0.11 worse for chemotherapy group in adjusted model).

Conclusions: There was no evidence of cognitive decline associated with chemotherapy in this sample of older adults with breast and colorectal cancer.

Key Words: breast cancer, cancer survivors, colorectal cancer, cognition, chemotherapy, cancer care

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In the United States alone, there are currently >11 million cancer survivors.[1,2] This makes the long-term consequences of cancer treatments an area of substantial public health concern.[3–5] Several studies have shown declines in self-reported cognitive functioning after chemotherapy[6,7]; however, research on the effect of chemotherapy on neuropsychological tests has been mixed.[8,9] Some prominent studies have shown small-to-moderate negative effects of chemotherapy on measures of memory and executive functioning,[10–18] whereas others have shown no chemotherapy-based cognitive declines.[19–24] However, these studies have primarily included younger women.

Older adults are at an increased risk of dementia,[25] and having cancer is a risk factor for long-term cognitive deficits.[26,27] Thus, chemotherapy could have a greater effect on cognitive function in older adults. Yet, few studies to date have examined older adults, and the results of these studies have been mixed.[28,29] Given that older adults with cognitive impairment require greater care[30] and have higher mortality rates,[31] there is a great need to establish whether chemotherapy has enduring cognitive side effects in older adults.

To address this need, we took advantage of a unique, prospectively collected assessment of cognitive function in the Health and Retirement Study (HRS) linked to Medicare claims data to test 2 hypotheses about the long-term effect of chemotherapy on cognitive functioning. First, we tested the

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hypothesis that for patients who receive chemotherapy, the rate of cognitive decline after treatment would be greater than their rate of cognitive decline before the receipt of chemotherapy. Second, we hypothesized that the rate of cognitive decline after diagnosis would be greater for patients who receive chemotherapy than for cancer patients who did not have chemotherapy while simultaneously controlling for other risk factors for cognitive decline.

METHODS

Settings and Participants

The HRS is a longitudinal panel study that surveys a nationally representative sample of Americans over the age of 50 every 2 years about a wide array of topics, including detailed questions about their cognitive function.[32] On turning 65, most of the cohort consented to link their Medicare administrative data with the HRS interview data.

We examined all respondents who had cognitive testing in the HRS-Medicare cohort between 1998 and 2004. Within this group, we identified patients with incident breast or colorectal cancer using Medicare claims from 1998 through 2006. We chose to focus on these 2 types of cancer because of their high incidence and high survivability. Incident breast cancer cases were identified via the validated Nattinger algorithm.[33,34] Incident colorectal cancer cases were defined by the method of Yabroff,[35] where we excluded prevalent cases by requiring no previous colorectal cancer claims in the prior 1095 days.[36]

Chemotherapy was defined by the presence of claims for chemotherapy infusion, using a validated method.[37] Outpatient chemotherapy was defined for both types of cancer by the occurrence of Healthcare Common Procedure Coding System codes in an outpatient or carrier file or the inpatient file; the relevant codes are included in Supplemental Digital Content 1, http://links.lww.com/MLR/A303. These codes were identified by independent review of all Medicare-covered infusion drugs by a medical oncologist (J.J.G.) and an internist (T.J.I.).

We required at least 1 cognitive status examination before diagnosis and continuous enrollment in fee-for-service Medicare, to ensure full claims data were present. Date of diagnosis was inferred as the earliest inpatient or outpatient claim date associated with cancer. The time between diagnosis and the last cognitive status examination before diagnosis varied by respondent; median length was 360 days, with a range of 2 to 3394 days. All patients were followed through death or the 2006 HRS survey. These inclusion criteria resulted in a minimum of 1 observation (before cancer diagnosis) and a maximum of 6 observations per respondent. Observations were collected every 2 years resulting in a maximum follow-up time of 9 years (eg, patient diagnosed in 1998 immediately after 1998 observation with follow-up data from 2000 to 2006 collected every 2 y). The timing of diagnosis varied between patients ranging from 5 observations before diagnosis and 1 after to 1 observation before diagnosis to 5 after.

Outcomes

Cognitive function was measured using a modified version of the Telephone Interview for Cognitive Status (TICS-m), which was developed from 2 well-validated scales: (1) the original TICS measure and (2) the Mini-Mental State Examination. The TICS-m, validated on large nationally representative samples, has been shown to have satisfactory psychometric properties and to correlate with important sociodemographic and health characteristics in predictable ways[38,39] and has been successfully used to document the effects of other diseases on long-term cognitive function.[40,41] More information on the HRS cognitive scale is available at the HRS Web site.[42] HRS respondents represented by a proxy are not administered the cognitive scale. Therefore, data from proxies were excluded from our primary analysis, resulting in the loss of 8% of all observations. Using data for the full HRS sample, we calculated that among 65-year-olds, TICS-m scores declined by an average of 0.55 points over 3 years, by 0.92 points over 5 years, and by 1.84 points over 10 years, or approximately 0.18 points per year. Using this pattern of cognitive decline for "normal aging," we defined a change of 0.4 points per year as the minimum clinically significant change in TICS-m scores, with lower scores indicating declines in cognitive function. This magnitude of change would indicate that 1 year of cognitive decline due to chemotherapy approximates 2 years of "normal" cognitive decline.

Analyses

To examine the impact of chemotherapy on cognitive functioning, we studied the psychometric properties of the TICS-m for our specific population of interest (individuals in the HRS with breast or colorectal cancer). We then estimated several hierarchical longitudinal models of patients' TICS-m scores, which allow these scores to have one pattern of change before diagnosis and a second pattern of change after diagnosis. These models used TICS-m score as the outcome and time, diagnosis (before/after), and chemotherapy receipt (receive/did not receive) as predictors. To develop the unadjusted model, we tested several linear and nonlinear hierarchical longitudinal models that included these predictor variables and their interactions. Models were assessed using the restricted maximum likelihood estimate with the lme4 package in R[43] and using the Markov chain Monte Carlo method with the rjags package in R.[44] The best model, as judged by AIC (Akaike Information Criterion), BIC (Bayesian Information Criterion), and deviance, is described and expanded upon below; our results were not sensitive to model choice. After the selection of the best fitting unadjusted model, we estimated the same model while adjusting for effects of age, body mass index, Charlson score, activities of daily living, instrumental activities of daily living, education, income, tobacco and alcohol use, and census region. The covariates were chosen because of their known relationships with cognitive functioning and/or administration of chemotherapy.[38,45,46] In the adjusted model, the covariates were treated as fixed-effects, and effects were estimated separately on the slope and on the intercept of the growth curve as well as on the interaction between chemotherapy receipt and time. For all models, we used one-tailed

tests of the hypothesis that chemotherapy is associated with declines in cognitive function; therefore we report only the lower bound of all posterior intervals.

In addition to these primary analyses, we replicated 4 versions of this model to determine whether our conclusions were robust to a variety of confounders. We tested (1) whether the exclusion of proxies influenced our results by setting cognition score to zero when a proxy was used, (2) whether the chemotherapy group was substantively different from the control group before treatment using a propensity matching approach, (3) whether only short-term effects of chemotherapy existed by analyzing only the observation immediately after diagnosis, and (4) whether a continuous or categorical interpretation of the TICS-m affected the results. We also used data simulation to estimate the probability of obtaining our results, assuming existence of a minimum clinically significant change on the TICS-m defined above. That is, we estimated the probability that we would obtain the reported results if chemotherapy truly decreased cognitive function by 0.4 points per year. This is essentially a post hoc power calculation under the hypothesis of a minimum clinically significant change. Details of these models are presented in Appendix.

In the frequentist analyses, a *P*-value of 0.05 was considered significant. Because we also estimated Bayesian models, we report 95% posterior intervals (PI) rather than confidence intervals, although they are similar in that both provide ranges of plausible values for the parameter tested.

This work was approved by the University of Michigan Institutional Review Board. Participants provided informed consent on enrollment in the HRS and again for linkage to Medicare claims.

RESULTS

Of the 16,772 respondents in the HRS-Medicare data, we identified 141 breast and 224 colorectal cancer patients with incident disease between 1998 and 2006, 24% (n = 88) of whom received chemotherapy. Of the 365 patients, only 255 had cognitive status examinations after diagnosis (61 of chemotherapy patients had cognitive examinations). Those patients were followed for a median of 3.1 years after diagnosis and up to 8.3 years afterwards. There were few significant differences between the chemotherapy and non-chemotherapy groups before diagnosis; Table 1. Figure 1 depicts the mean TICS-m score at each observation for the chemotherapy and no chemotherapy groups. Negative numbers represent observations before diagnosis, and positive numbers represent observations after diagnosis. Very few patients have >3 observations before or after diagnosis. Therefore, Figure 1 was limited to 3 observations before and after diagnosis. Both groups exhibited declines in cognitive functioning at a rate of 0.27 points per year before diagnosis ($P < 0.01$, 95% PI: −0.29, −0.14) with no significant difference in rate of change between patients who eventually received chemotherapy and those who did not ($P = 0.28$, 95% PI: −0.13, 0.33).

As applied to the current population, we studied the psychometric properties of the TICS-m by fitting a 1-factor model to the 4 items making up the scale. In this analysis, we used all data observed at the wave immediately before individuals' cancer diagnosis. In fitting the 1-factor model to the data, we rejected the hypothesis of exact fit ($\chi^2(2) = 10.5$, $P < 0.05$). The hypothesis of exact fit is often rejected at larger sample sizes, so we also examined the Root Mean Square Error of Approximation (RMSEA). The 90% confidence interval for the RMSEA was (0.053, 0.184), which implies a range from "reasonable fit" to "poor fit."[47] The proportion of explained common variance was 0.65, Cronbach's

TABLE 1. Sample Characteristics at Observation Before Breast or Colorectal Cancer Diagnosis

	Chemotherapy (88)		No Chemotherapy (277)	
Patient Characteristics	**Breast (24)**	**Colorectal (64)**	**Breast (117)**	**Colorectal (160)**
Age*				
Mean (SD)	70.5 (5.3)	72.4 (7.9)	75.8 (7.5)	77.3 (9)
Median	69.3	72	75.7	79.6
Charlson score†				
Mean (SD)	0.8 (1.4)	1.2 (1.7)	1.2 (1.4)	2.2 (2.6)
Median	0	1	1	2
TICS-m score‡				
Mean (SD)	15.8 (4.1)	14.8 (4.6)	15.3 (4.3)	13.4 (4.1)
Median	17	15	16	13
ADL, n (%)				
No limitations before cancer	21 (88%)	50 (78%)	91 (78%)	107 (67%)
Limitations before cancer	3 (12%)	14 (22%)	26 (22%)	53 (33%)
Instrumental ADL, n (%)				
No limitations before cancer	22 (92%)	54 (84%)	102 (87%)	120 (75%)
Limitations before cancer	2 (8%)	10 (16%)	15 (13%)	40 (25%)
Education, n (%)§				
High school or less	8 (33%)	23 (36%)	24 (21%)	51 (32%)
Some college	5 (21%)	17 (27%)	53 (45%)	70 (44%)
College graduate	11 (46%)	24 (38%)	40 (34%)	39 (24%)
Tobacco user, n (%)				
Never	13 (54%)	25 (39%)	60 (51%)	71 (44%)
Former	7 (29%)	30 (47%)	40 (34%)	69 (43%)
Current	4 (17%)	9 (14%)	16 (14%)	18 (11%)
Missing	0 (0%)	0 (0%)	1 (1%)	2 (1%)
Alcohol, n (%)				
0 d/wk	18 (75%)	49 (77%)	79 (68%)	125 (78%)
<1 d/wk	0 (0%)	3 (5%)	10 (9%)	9 (6%)
1–2 d/wk	2 (8%)	3 (5%)	3 (3%)	3 (2%)
>2 d/wk	4 (17%)	9 (14%)	25 (21%)	23 (14%)
Census region, n (%)				
1	2 (8%)	11 (17%)	23 (20%)	26 (16%)
2	6 (25%)	24 (38%)	29 (25%)	53 (33%)
3	13 (54%)	25 (39%)	46 (39%)	62 (39%)
4	3 (12%)	4 (6%)	19 (16%)	19 (12%)
Net worth				
Mean	907	303	443	276
Median	213	162	184	96

Chemotherapy and no chemotherapy groups differed significantly in:
*Age, $t(363) = 4.83$, $P < 0.001$.
†Charlson score, $t(363) = 2.62$, $P = 0.01$.
‡Lower scores on the TICS indicate declines in cognitive function.
§Education, $\chi^2(2) = 10.6$, $P = 0.005$.
ADL indicates activities of daily living, TICS, Telephone Interview for Cognitive Status.

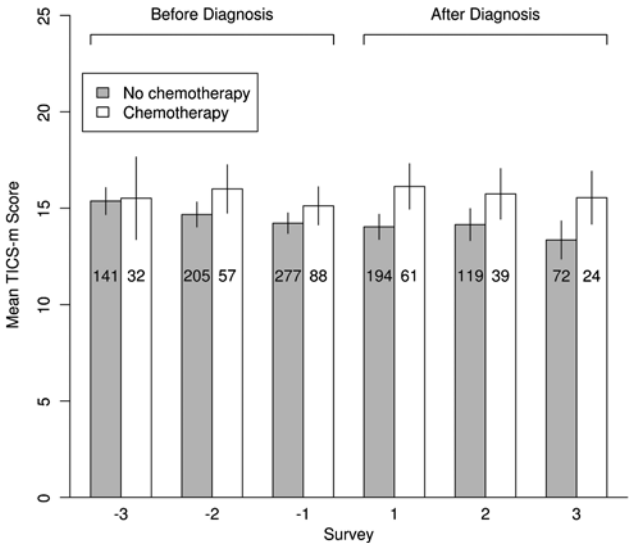

FIGURE 1. Mean cognition score by survey. Error bars indicate 95% confidence intervals for the SEM. These unadjusted results show no evidence of greater decline in the group of patients who received chemotherapy than those who did not. The numbers on each bar represent the number of patients contributing data to the observation.

TABLE 2. Parameter Estimates for the Adjusted Hierarchical Longitudinal Model of TICS-m Scores

Parameters	β	SE	*P*
Intercept	5.05	3.25	0.12
Time	−0.12	0.04	0.00
Chemotherapy receipt	0.52	0.45	0.25
Body mass index	1.75	0.96	0.07
Charlson score	−0.42	0.35	0.23
ADL	−0.16	0.27	0.56
Instrumental ADL	−0.61	0.31	0.05
Age	−0.15	0.02	0.00
Education			
High school or less	Reference		
Some college	2.42	0.44	0.00
College graduate	3.54	0.46	0.00
Tobacco user			
Never	Reference		
Former	−0.22	0.37	0.54
Current	0.64	0.53	0.22
Alcohol			
0 d/wk	Reference		
<1 d/wk	0.46	0.38	0.22
1–2 d/wk	−0.23	0.52	0.66
>2 d/wk	0.18	0.34	0.60
Census region			
1	Reference		
2	−0.29	0.48	0.56
3	−0.40	0.47	0.39
4	0.04	0.59	0.94
Net worth	0.17	0.05	0.00
Interactions			
Time × chemotherapy receipt*	0.11	0.10	0.86
Time × chemotherapy receipt × diagnosis†	0.17	0.17	0.84

*Term tests whether the change in TICS-m score over time is a function of chemotherapy receipt.

†Term tests whether the differences in the slope of TICS-m scores before or after cancer diagnosis is a function of chemotherapy receipt. TICS-m scores are allowed to have different slopes before and after diagnosis.

ADL indicates activities of daily living, TICS, Telephone Interview for Cognitive Status.

α was 0.62, and the corrected item-total correlations ranged from 0.33 to 0.86. The misfit was mainly due to 2 tasks (serial 7 and backwards counting) that accounted for only 7 points on the 27-point scale, so we elected to use the full scale in the analyses below. However, the substantive results described below hold for each of the 4 individual items making up the TICS-m.

We used 2 strategies to test for the presence of chemotherapy-associated cognitive declines. First, using a prospective approach, we compared rates of decline in cognitive function before and after diagnosis for patients receiving chemotherapy and found no significant differences in either the unadjusted ($P = 0.86$, one-sided 95% PI lower bound: 0.12 worse for chemotherapy group) or adjusted models ($P = 0.86$, one-sided 95% PI lower bound: 0.09 worse for chemotherapy group). Second, using a cohort approach, we compared rates of decline in cognitive function after diagnosis between those who received chemotherapy and those who did not. We found no significant differences in either the unadjusted ($P = 0.85$, one-sided 95% PI lower bound: 0.12 worse for chemotherapy group) or the adjusted models ($P = 0.84$, one-sided 95% PI lower bound: 0.11 worse for chemotherapy group) (Table 2). We also estimated the adjusted model with the entire HRS-cohort and found that cognitive function declined at a rate of 0.28 points per year ($z = -8.8$, $P < 0.05$, SE = 0.03); this value was very similar to the rate of change for cancer patients.

Our results were robust to a variety of confounders. First, instead of excluding proxies in the analyses, we included proxies in the sample and set their cognitive function scores to zero, thereby allowing us to test whether excluding proxies gave an unfair advantage to the null hypothesis. Even in such an extreme case, the model still ruled out all chemotherapy-based cognitive declines ($P = 0.95$, one-sided 95% PI lower bound: 0.08 better for chemotherapy group). In fact, nonchemotherapy patients utilized proxy respondents more often, so if proxy use was informative about poor cognitive functioning, it would provide yet stronger evidence against a chemotherapy-associated decline. In addition, we considered the possibility that (1) the chemotherapy group was substantively different from the control group, (2) chemotherapy affected cognitive function only at the first observation after diagnosis, and (3) categorical measures of cognitive function would yield different results than our continuous measure. We used 3 additional modeling approaches to test these alternative explanations, Supplemental Digital Content 2–5, http://links.lww.com/MLR/A304. The same general pattern emerged across all models: with 95% certainty, we can exclude declines in cognitive function associated with chemotherapy that are >1 year of "normal aging."

Finally, using the data simulation method described above, we calculated the probability of obtaining these results if chemotherapy truly decreased cognitive function by 0.4 points per year (the minimum clinically significant

change). In doing so, we were able to reject the hypothesis that chemotherapy induces cognitive declines of at least that magnitude with a certainty of $P = 0.05$.

DISCUSSION

In this study, which used a prospectively collected assessment of cognitive function in the HRS linked with Medicare claims data, we did not find support for either of our hypotheses. The rate of cognitive decline after diagnosis did not differ from the rate of cognitive decline before diagnosis for older Americans with breast or colorectal cancer. Moreover, the rate of cognitive decline after cancer diagnosis did not differ between patients who had chemotherapy and those who did not. These results were robust in several sensitivity analyses, and the likelihood of obtaining these results if clinically significant chemotherapy-based cognitive declines truly exist was 5%.

Our findings are in contrast to a number of cross-sectional studies, which have reported small-to-moderate effects of chemotherapy on cognitive functioning.[10–18,48–51] However, these results are in line with other prospective studies that have shown no long-term impact of chemotherapy on cognitive function.[19–24,48–51] In addition to extending the findings of other prospective studies to a new measure of cognitive function, the HRS-Medicare data address the collective weaknesses of prior prospective studies: a lack of data on cognitive function before diagnosis, limited data on cognitive function after treatment, short follow-up periods, and statistical models that do not include longitudinal components or individual differences.

There are some limitations of using the TICS-m to measure cognitive function: (1) the TICS-m is a cognitive screening measure not a full cognitive assessment; as such, it is less sensitive to small changes in cognitive function. Yet it has been successfully used to document the effects of other diseases on long-term cognitive function[40,41]; (2) given the somewhat less than optimal reliability estimates in combination with relatively small sample sizes, the possibility of lower detectable effect sizes cannot be ruled out; (3) the TICS-m largely measures memory and attention[52]; additional research is needed to determine whether long-term declines exist in other domains of cognitive function. There are also several limitations specific to the use of Medicare administrative data: (1) Medicare data were only available for consenting participants, which could bias our results; (2) although we used validated algorithms to detect cancer cases in Medicare, this is not the same as clinical assessment; (3) we were unable to assess second primaries or recurrences in the chemotherapy-treated group; (4) stage of disease is not available in the claims data. More generally, this sample only includes patients with breast and colorectal cancer; therefore, generalizations of these findings to other types of cancer treated with other types of chemotherapy may be limited. We were also unable to examine type or duration of chemotherapy with this sample size. Although there may be subpopulations at greater risk for adverse cognitive effects of chemotherapy,[16,17] our analysis speaks to the lack of an association at the population level. However, we believe the merits of a longitudinal design with cognitive data collected before cancer diagnosis outweigh the limitations.

In addition to patient clinical factors and cancer characteristics factors, chemotherapy decisions also include a consideration of potential treatment toxicity and patient willingness to experience that toxicity for, on occasion, uncertain benefit.[53] Given the importance that patients place on preservation of cognitive function when weighing treatment decisions,[54] the information garnered from this study may be useful to patients and physicians alike. Using a prospectively collected assessment of cognitive function, we found no evidence of clinically significant declines in memory and attention due to chemotherapy. Therefore, concerns about chemotherapy commonly reported in the media may not be justified for most older breast and colorectal cancer patients.[4,5]

APPENDIX

We replicated several versions of this model to determine whether our conclusions were robust to a variety of confounders. First, we considered the fact that excluding proxies from our sample may have given an unfair advantage to the null hypothesis if there were a proportionally greater number of proxy respondents in the chemotherapy group. To address this, we replicated the adjusted model while including proxies in the sample and setting their cognition scores to zero every time a proxy was used. Second, we considered the possibility that the chemotherapy group was substantively different from the control group before treatment. To account for this, we created propensity scores for obtaining chemotherapy for each individual using all covariates from the observation immediately before diagnosis. Minimum distance matched sampling[55] was then carried out, yielding a matched control patient for each chemotherapy patient. We then tested for chemotherapy-based cognitive declines by comparing cognition scores from patients that received chemotherapy to the newly created matched cohort. Third, we considered the possibility that chemotherapy-based cognitive declines only arise immediately after diagnosis (ie, the patient takes an initial "hit" and then recovers). To test for short-term chemotherapy-related declines in cognition scores, we estimated the original adjusted model including only the first observation after diagnosis for each chemotherapy patient. Fourth, we examined whether using a continuous or categorical measure of cognition score affected interpretations of the findings. The original, adjusted model used a continuous measure of cognition. Therefore we fit an additional hierarchical ordinal logistic regression (ie, proportional odds) model to a trichotomous cognition measure (normal cognitive functioning, cognitive impairment without dementia, or dementia). The cut points used to create these categories were based on prior studies with the HRS data.[56–58] Normal was defined as 8–27; cognitive impairment without dementia was 6–7; and dementia was 0–5. The covariates in the model were the same as the original, adjusted model.

We also used data simulation to estimate our ability to detect a chemotherapy-associated decrease in cognition scores

of 0.4 points per year, which was defined as the minimum clinically significant change on this measure of cognitive functioning. To do so, we treated all estimates from our adjusted model (ie, the modeling including covariates) as parameters, with the exception of the estimated effect of chemotherapy, which we set to the minimum clinically significant value of a decline in cognition score of 0.4 points per year. We then generated 5000 datasets from this model. All generated datasets matched our observed data on number of patients, time at which each patient was observed, and number of patients receiving chemotherapy. We then fit the hierarchical model described above to each of our 5000 generated datasets, recording the size of the estimated effect of chemotherapy on cognitive functioning for each dataset. We then determined the proportion of times we observed an estimate of chemotherapy-based cognitive decline as extreme or greater than that observed in our adjusted model. In doing so, this analysis provides the probability of obtaining the reported results if chemotherapy truly decreased cognitive function by 0.4 points per year (the minimum clinically significant change).

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2008*. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2008/.
2. Stat bite: cancer survivors in the United States. *J Natl Cancer Inst*. 2008;100:236.
3. Hewitt M, Greenfield S, Stovall E. *From Cancer Patient to Cancer Survivor: Lost in Translation*. Washington, DC: National Academies Press; 2006.
4. Gross J. Chemotherapy fog is no longer ignored as an illusion. *New York Times*. April 29, 2007. Available at: http://nytimes.com/2007/04/29/health/29chemo.html. Accessed November 17, 2010.
5. Brody JE. The fog that follows chemotherapy. *New York Times*. August 3, 2009. Available at: http://www.nytimes.com/2009/08/04/health/04brod.html?_r=1. Accessed December 13, 2010.
6. Boykoff N, Moieni M, Subramanian SK. Confronting chemobrain: an in-depth look at survivors' reports of work, social networks, and health care response. *J Cancer Surviv*. 2009;3:223–232.
7. Mehnert A, Scherwath A, Schirmer L, et al. The association between neuropsychological impairment, self-perceived cognitive deficits, fatigue and health related quality of life in breast cancer survivors following standard adjuvant versus high-dose chemotherapy. *Patient Educ Couns*. 2007;66:108–118.
8. Soussain C, Ricard D, Fike JR, et al. CNS complications of radiotherapy and chemotherapy. *Lancet*. 2009;374:1639–1651.
9. Correa DD, Ahles TA. Neurocognitive changes in cancer survivors. *Cancer J*. 2008;14:396–400.
10. Ahles TA, Saykin A. Cognitive effects of standard-dose chemotherapy in patients with cancer. *Cancer Invest*. 2001;19:812–820.
11. Ahles TA, Saykin AJ, Furstenburg CT, et al. Neuropsychological impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol*. 2002;20:485–493.
12. Wefel JS, Lenzi R, Theriault RL, et al. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma. *Cancer*. 2004;100:2292–2299.
13. Quesnel C, Savard J, Ivers H. Cognitive impairments associated with breast cancer treatments: results from a longitudinal study. *Breast Cancer Res Treat*. 2009;116:113–123.
14. Weis J, Poppelreuter M, Bartsch HH. Cognitive deficits as long-term side effects of adjuvant therapy in breast cancer patients: "subjective" complaints and "objective" neuropsychological test results. *Psychooncology*. 2009;18:775–782.
15. Wefel JS, Saleeba AK, Buzdar AU, et al. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. *Cancer*. 2010;116:3348–3356.
16. Ahles TA, Saykin AJ, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *J Clin Oncol*. 2010;28:4434–4440.
17. Janelsins MC, Kohli S, Mohile SG, et al. An update on cancer- and chemotherapy-related cognitive dysfunction: current status. *Semin Oncol*. 2011;38:431–438.
18. Phillips KM, Jim HS, Small BJ, et al. Cognitive functioning after cancer treatment: a 3-year longitudinal comparison of breast cancer survivors treated with chemotherapy or radiation and noncancer controls. *Cancer*. 2012;118:1925–1932.
19. Donovan KA, Small BJ, Andrykowski MA, et al. Cognitive functioning after adjuvant chemotherapy and/or radiation for early-stage breast cancer. *Cancer*. 2005;104:2499–2507.
20. Jenkins V, Shilling V, Deutsch G, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *Br J Cancer*. 2006;94:828–834.
21. Jim HSL, Donovan KA, Small BJ, et al. Cognitive functioning in breast cancer survivors: a controlled comparison. *Cancer*. 2009;115:1776–1783.
22. Mehlsen M, Pedersen AD, Jensen AB, et al. No indications of cognitive side-effects in a prospective study of breast cancer patients receiving adjuvant chemotherapy. *Psychooncology*. 2009;18:248–257.
23. Debess J, Riis JØ, Engebjerg MC, et al. Cognitive function after adjuvant treatment for early breast cancer: a population-based longitudinal study. *Breast Cancer Res Treat*. 2010;121:91–100.
24. Tager FA, McKinley PS, Schnabel FR, et al. The cognitive effects of chemotherapy in post-menopausal breast cancer patients: a controlled longitudinal study. *Breast Cancer Res Treat*. 2010;123:25–34.
25. Plassman B, Langa K, Fisher G, et al. Prevalence of cognitive impairment without dementia in the United States. *Ann Intern Med*. 2008;148:427–434.
26. Helfin LH, Meyerowitz BE, Hall P, et al. Cancer as a risk factor for long-term cognitive deficits and dementia. *J Natl Cancer Inst*. 2005;97:854–856.
27. Khan NF, Mant D, Carpenter L, et al. Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. *Br J Cancer*. 2011;105:S29–S37.
28. Baxter NN, Durham SB, Phillips KA, et al. Risk of dementia in older breast cancer survivors: a population-based cohort study of the association with adjuvant chemotherapy. *J Am Geriatr Soc*. 2009;57:403–411.
29. Heck JE, Albert SM, Franco R, et al. Patterns of dementia diagnosis in surveillance, epidemiology, and end results breast cancer survivors who use chemotherapy. *J Am Geriatr Soc*. 2008;56:1687–1692.
30. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet*. 1997;349:1793–1796.
31. Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. *Int J Geriatr Psychiatry*. 2001;16:751–761.
32. Health and Retirement Study. Available at: http://hrsonline.isr.umich.edu/. Accessed December 8, 2011.
33. Nattinger AB, Laud PW, Bajorunaite R, et al. An algorithm for the use of Medicare claims data to identify women with incident breast cancer. *Health Serv Res*. 2004;39(pt 1):1733–1749.
34. Gold HT, Do HT. Evaluation of three algorithms to identify incident breast cancer in Medicare claims data. *Health Serv Res*. 2007;42:2056–2069.
35. Yabroff KR, Warren JL, Banthin J, et al. Comparison of approaches for estimating prevalence costs of care for cancer patients: what is the impact of data source? *Med Care*. 2009;47(suppl 1):S64–S69.
36. McBean AM, Warren JL, Babish JD. Measuring the incidence of cancer in elderly Americans using Medicare claims data. *Cancer*. 1994;73:2417–2425.
37. Lamont EB, Herndon JE III, Weeks JC, et al. Criterion validity of Medicare chemotherapy claims in Cancer and Leukemia Group B breast and lung cancer trial participants. *J Natl Cancer Inst*. 2005;97:1080–1083.
38. Herzog AR, Wallace RB. Measures of cognitive functioning in the AHEAD Study. *J Gerontol B Psychol Sci Soc Sci*. 1997;52(special no.):37–48. 20.

39. Welsh KA, Breitner JCS, Magruder-Habib KM. Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol*. 1993;6:103–110.
40. Iwashyna TJ, Ely EW, Smith DM, et al. Long term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304:1787–1794.
41. Khatri M, Nickolas T, Moon YP, et al. CKD associates with cognitive decline. *J Am Soc Nephrol*. 2009;20:2427–2432.
42. Ofstedal MB, Fisher GG, Herzog AR. Documentation of Cognitive Functioning Measures in the Health and Retirement Study; 2005. Available at: http://hrsonline.isr.umich.edu/sitedocs/userg/dr-006.pdf. Accessed November 17, 2010.
43. Bates D, Maechler M. (2010). lme4: linear mixed-effects models usingS4 classes. R package version 0.999375-34. Available at: http://CRAN.R-project.org/package = lme4. Accessed June 1, 2012.
44. Plummer M 2010. rjags: Bayesian graphical models using MCMC. R package version 2.1.0-5. Available at: http://CRAN.R-project.org/package = rjags. Accessed June 1, 2010.
45. Griggs JJ, Sorbero MES, Lyman GH. Undertreatment of obese women receiving breast cancer chemotherapy. *Arch Intern Med*. 2005;165:1267–1273.
46. Griggs JJ, Culakova E, Sorbero MES, et al. Effect of patient socioeconomic status and body mass index on the quality of breast cancer adjuvant chemotherapy. *J Clin Oncol*. 2007;25:277–284.
47. Browne MW, Cudeck R. Alternative ways of assessing model fit. In: Bollen KA, Long JS, eds. *Testing Structural Equation Models*. Newbury Park, CA: Sage; 2005:136–162.
48. Anderson-Hanley C, Sherman ML, Riggs R, et al. Neuropsychological effects of treatments for adults with cancer: a meta-analysis and review of the literature. *J Int Neuropsychol Soc*. 2003;9:967–982.
49. Faletti MG, Sanfilippo A, Maruff P, et al. The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. *Brain Cogn*. 2005;59:60–70.
50. Jansen CE, Miaskowski C, Dodd M, et al. A metaanalysis of studies of the effects of cancer and chemotherapy on various domains of cognitive function. *Cancer*. 2004;104:2222–2233.
51. Stewart A, Bielajew C, Collins B, et al. A meta-analysis of the neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer. *Clin Neuropsychol*. 2006;20:76–89.
52. Crooks VC, Petitti DB, Robins SB, et al. Cognitive domains associated with performance on the Telephone Interview for Cognitive Status-modified. *Am J Alzheimers Dis Other Demen*. 2006;21:45–53.
53. Jansen SJ, Otten W, Stiggelbout AM. Review of determinants of patients' preferences for adjuvant therapy in cancer. *J Clin Oncol*. 2004;22:3181–3190.
54. Fried TR, Bradley EH, Towle VR, et al. Understanding the treatment preferences of seriously ill patients. *N Engl J Med*. 2002;346:1061–1066.
55. Rosenbaum PR, Ross RN, Silber JH. Minimum distance matched sampling with fine balance in an observational study of treatment for ovarian cancer. *J Am Stat Assoc*. 2007;102:75–83.
56. Langa KM, Chernew ME, Kabeto MU, et al. National estimates of the quantity and cost of informal caregiving for the elderly with dementia. *J Gen Intern Med*. 2001;16:770–778.
57. Langa KM, Larson EB, Karlawish JH, et al. Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? *Alzheimers Dement*. 2008;4:134–144.
58. Alzheimer's Association. Early onset dementia: a national challenge, a future crisis; 2006. Available at: http://www.alz.org/national/documents/report_earlyonset_full.pdf. Accessed December 1, 2011.

