Relationship Between Chemotherapy Use and Cognitive Impairments in Older Women With Breast Cancer

Findings From a Large Population-Based Cohort

Xianglin L. Du, MD, PhD, Rui Xia, MS,* and Dale Hardy, PhD**

Background: Several small scale clinical trials indicated a possible relationship between chemotherapy administration and the increased risk of cognitive impairments in patients with breast cancer, but little information was available from large population-based cohort studies.

Methods: We studied 62,565 women who were diagnosed with stages I-IV breast cancer at age ≥65 years from 1991 through 2002 from 16 regions in the Surveillance, Epidemiology and End Results program who were free of cognitive impairments at diagnosis with up to 16 years of follow-up, and also studied 9752 matched cohort based on the propensity of receiving chemotherapy. The cumulative incidence of cognitive impairments was calculated and the time to event (cognitive impairments) analysis was conducted using Cox hazard regression model.

Results: Overall, patients who received chemotherapy were 8% more likely to have drug-induced dementia compared with those without chemotherapy, but that was not statistically significant after adjusting for patient and tumor characteristics (hazard ratio = 1.08, 95% confidence interval = 0.85–1.37). The risk of developing Alzheimer disease, vascular dementia, or other dementias was significantly lower in patients receiving chemotherapy except for cognitive disorder which was not significantly different between the 2 chemotherapy groups. The results were somewhat similar in the entire cohort and the matched cohort based on the probability of receiving chemotherapy.

Conclusion: There was no significant association between chemotherapy and the risk of developing drug-induced dementia and unspecified cognitive disorders. The risk of developing Alzheimer disease, vascular dementia, or other dementias was significantly lower in patients receiving chemotherapy. This study with long-term follow-up did not support the findings that chemotherapy was associated with an increased risk of late stage cognitive impairments.

Key Words: chemotherapy, dementia, cognitive impairments, older women, breast cancer

(*Am J Clin Oncol* 2010;33: 533–543)

Chemotherapy has been documented to be efficacious in treating women with breast cancer over the past several decades.[1–3] The use of such a therapy increased over time in the early 1990s,[4–6] and the trend is likely to continue because the National Institutes of Health Consensus Statement in November 2000 recommends that women with tumor size of more than 1 cm be treated with adjuvant chemotherapy regardless of lymph node positivity status.[7] Many physicians and researchers advocate chemotherapy for all patients with breast cancer including those with small tumor of less than 1 cm. For women aged 70 or older, the guideline on the use of chemotherapy was less clear and because they were more likely to receive hormone therapy.[7]

However, what has not been well investigated is the possible relationship between cognitive impairments and chemotherapy administration in patients treated with chemotherapy. There were some anecdotal reports in the 1980s, indicating that patients treated with chemotherapy complained of changes or difficulties in their memory, attention, concentration, and language skills.[8–11] Studies of neurocognitive late effects of cancer therapies were shown in children,[12,13] but studies in adults are sparse and have focused primarily on patients receiving cranial irradiation, especially those with small cell lung cancer.[14–18] The first study to address this relationship within context of a randomized trial for patients with breast cancer was reported by van Dam et al in 1998.[19] In the treatment group, they administered 4 cycles of combination chemotherapy agents of fluorouracil, epidoxorubicin, and cyclophosphamide; and a fifth course of high-dose combination chemotherapy (cyclophosphamide and carboplatin) with autologous hematopoietic progenitor cell support.[19] The subsequent reports on the positive relationship between cognitive decline and chemotherapy use from the investigators reinforced the original findings.[20–24] Two recent small scale randomized trials by Brezden et al[25] and Wefel et al[26] found a similar finding, ie, the receipt of chemotherapy was moderately associated with the early stage cognitive impairments.[25,26]

However, it might be difficult to find an "ideal" control group in clinical trials, because it would be unethical to randomize those women who are candidates for adjuvant chemotherapy into the control group without chemotherapy. Additionally, because randomized clinical trials often have strict enrollment criteria with close monitoring and follow-up among volunteers, one might expect differences in cognitive dysfunctions in the community comparing with that in clinical trials. The large population-based observational study could provide findings that cannot be answered by clinical trials, but little information was available from population-based study looking at the relationship between chemotherapy and the risk of dementia.[27,28] Heck et al[27] found that patients who received chemotherapy were more likely to be diagnosed with dementia (hazard ratio = 1.20) after adjusting for propensity score. Hurria et al[28] studied 31 women with breast cancer prospectively and found that subset of these women experienced a decline in cognitive function. Beyond the scope of the above reports, our study aimed to differentiate 5 types of cognitive impairments, including Alzheimer disease, vascular dementia, amnestic disorder, drug-induced dementia and psychoses, and other dementia or cognitive disorders that are not specified, in a larger population-based cohort of patients with breast cancer with up to 16 years of follow-up. In addition, within this large cohort, we also performed additional matched-cohort analysis to verify our study findings and to assess the potential selection bias that might have explained the study findings. We hypothesize that there will not be a significant difference in the occurrence of any type of cognitive impairments in women diagnosed with breast

From the *School of Public Health, University of Texas Health Science Center, Houston, TX.

Supported by a grant from the Agency for Healthcare Research and Quality (R01-HS016743).

Reprints: Xianglin L. Du, MD, PhD, University of Texas School of Public Health, 1200 Herman Pressler Dr, RAS-E631, Houston, TX 77030. E-mail: xianglin.l.du@uth.tmc.edu.

ISSN: 0277-3732/10/3306-0533
DOI: 10.1097/COC.0b013e3181b9cf1b

cancer who received chemotherapy compared with women with breast cancer who did not use chemotherapy.

PATIENTS AND METHODS

Data Sources

We used the merged Surveillance, Epidemiology and End Results (SEER)-Medicare database for this analysis. The SEER program, supported by the National Cancer Institute, includes population-based tumor registries in selected geographic areas: San Francisco/Oakland, Detroit, Seattle, Atlanta, Rural Georgia, Los Angeles county, the San Jose-Monterey area, and the rest of California; and the states of Connecticut, Iowa, New Mexico, Utah, Hawaii, Kentucky, Louisianan, and New Jersey. The 4 registries from Kentucky, Louisiana, New Jersey, and greater California became available in 2000, thus increasing the coverage from 14% in 1991–1999 to 25% of the US population in 2000–2002.[26] These registries ascertain all newly diagnosed (incident) breast cancer cases from multiple reporting sources such as hospitals, outpatient clinics, laboratories, private medical practitioners, nursing/convalescent homes/hospices, autopsy reports, and death certificates.[29] Information includes tumor location, size, American Joint Committee on Cancer stage, tumor size, grade, and estrogen receptor status; demographic characteristics such as age, gender, race and marital status; and types of treatment provided within 4 months after the date of diagnosis.[29] The Medicare Program is administered by the Center for Medicare and Medicaid Services, and covers hospital, physician and other medical services for more than 97% of persons aged 65 years or older.[30] The Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston approved this study.

Study Population

The inclusion and exclusion criteria were to include subjects who had a complete coverage of Medicare claims, were free of cognitive impairments at the baseline, received chemotherapy as part of initial therapy within 12 months of diagnosis, and aged 65 to 89 years. The study population consisted of 79,512 women who were diagnosed with breast cancer as the only primary tumor at age ≥65 years from 1991 through 2002, and who had full coverage of Medicare part A and part B, and were not enrolled with Health Maintenance Organizations from the year of diagnosis to the last follow-up (December 2005 or date of death). Because of small numbers, cases from Atlanta and rural Georgia were combined. For the purpose of this study in determining the relationship between chemotherapy and cognitive impairments, we included only patients who were free of any cognitive impairment of the study outcomes at the time of cancer diagnosis, specifically drug-induced dementia and psychoses, Alzheimer disease, vascular dementia, amnestic disorder, and nonspecified dementia. By doing so, we excluded 4320 cases with preexisting cognitive impairments, 4752 cases who received first chemotherapy only after 12 months of diagnosis and 7875 patients aged 90 or older, leaving 62,565 subjects for the final analysis. We excluded those with chemo initiated after 12 months to minimize the confounding because of recurrence and related complications; and excluded those 90 or older because the number of cases was small and few cases received chemotherapy.

Matched Cohort

To minimize selection bias because of factors that may have influenced physicians or patients to choose chemotherapy, we first calculated the propensity (or conditional probability) of receiving chemotherapy for all patients, and then matched patients who actually received chemotherapy with those who had the same or similar propensity but did not receive chemotherapy. This approach could also help assess the extent of potential selection bias, if any, by comparing the results with that in the entire cohort. Because the propensity of receiving chemotherapy was almost identical between the 2 comparison groups, those patient characteristics or tumor factors (such as age, hormone receptor status, and comorbidity) can be relatively balanced between the chemotherapy and nonchemotherapy groups, therefore minimizing potential selection bias that may have explained the outcome differences. The propensity of receiving chemotherapy was created through the logistic regression model based on the following patient and tumor characteristics: age, ethnicity, marital status, tumor stage, tumor grade, tumor size, hormone receptor status, comorbidity, radiation therapy, socioeconomic status, year of diagnosis, and SEER areas. These characteristics were chosen in the model because they affected the choice of chemotherapy.[1–5] The matching through the 5→1 digit propensity of receiving chemotherapy was performed using the well validated greedy matching algorithm and the SAS Macro program by Parsons.[31] A total of 9752 patients receiving chemotherapy were matched with 9752 patients who did not receive chemotherapy.

Chemotherapy

The methods of identifying chemotherapy use through the Medicare claims was discussed elsewhere.[32,33] In brief, patients were defined as having received chemotherapy if there was a claim for chemotherapy from any of the following Medicare codes[34–36] that were made within 12 months of diagnosis: the ICD-9-CM procedure code of 9925 and V codes of V58.1, V66.2, or V67.2, the Common Procedure Terminology codes of 96400 to 96549, J8510, J8520, J8521, J8530 to J8999, J9000 to J9999, and Q0083 to Q0085, and revenue center codes of 0331, 0332, and 0335.

Cognitive Impairments

Cognitive impairment was defined if there were at least 2 claims that were 30 days apart for each of the following diagnoses (with ICD-9-CM codes)[34] after chemotherapy use: cognitive disorder, NOS (code 294.9), amnestic disorder (code 294.0), Alzheimer disease (code 331.0), vascular dementia (codes 290.×), dementia, NOS (code 294.8), or drug-induced dementia and psychoses (codes 292.×).

Mood Disorders

Mood disorder was defined if there were two claims that were 30 days apart for each of the following diagnoses (with ICD-9-CM codes)[34] before or after chemotherapy use: anxiety state, unspecified (code 300.0), anxiety depression (code 300.4), depressive disorder, NOS (codes 311.×), alteration of consciousness (code 780.9), and other depressions (codes 296.2, 296.3, 296.5, 296.6, 296.7, 298.0, 301.10, 301.12, 301.13, 309.0, 309.1).

Comorbidity Index

Comorbidity was ascertained from Medicare claims data through diagnoses or procedures that were made between 1 year before and 1 month after the diagnosis of breast cancer.[37–39] We included claims for comorbid diseases made within 1 month of diagnosis because any comorbid diseases present at that time would be likely to affect the choice of chemotherapy. We used the comorbidity index created by Charlson et al[40] and later modified by Romano et al[41] using the ICD-9-CM diagnosis and procedure codes.[42]

Analyses

Because SEER cancer registries reported only the month and year of diagnosis of breast cancer, we arbitrarily defined the day of diagnosis as the 15th of the month. For example, if a patient was diagnosed in March 1998, then the date of diagnosis was given as March 15, 1998. The χ^2 statistic was used to test the significance of having various cognitive impairments between women who received chemotherapy and those who did not in the entire cohort and in the

matched cohort. Incidence rate (density) was defined as the ratio of the number of new cognitive impairments over the total number of person-years. Person-years were calculated as the number of patients multiplied by the number of years from diagnosis to the date of the first cognitive impairment, or date of death, or date of last follow-up, whichever occurred first. The cumulative incidence (probability) of cognitive impairments was calculated using the statistical program by Penman and Johnson.[43] The time to event (cognitive impairment) analysis was conducted using the Cox proportional hazard regression model available in SAS.[44]

RESULTS

Table 1 presents the distribution of baseline characteristics among the entire cohort of patients with breast cancer stratified by the chemotherapy status and also presents the comparisons of the matched cohort based on propensity score. In the entire cohort, a higher proportion of younger patients and married women received chemotherapy. A slightly lower percentage of whites received chemotherapy. There was no significant difference across the quartiles of socioeconomic status. The higher percentage of not receiving chemotherapy was related to earlier stage, smaller tumor size, fewer positive lymph nodes, low grade tumors, and positive hormone receptor status. Patients with higher comorbidity scores were less likely to receive chemotherapy. A higher proportion of women who had mastectomy and radiation therapy received chemotherapy. The distribution of these characteristics was significantly different between patients receiving chemotherapy and those who did not. However, in the matched cohort, there was no significant difference in terms of socio-demographic and tumor factors (stage, size, and hormone receptor status) between the 2 groups according to chemotherapy status except for age.

Table 2 presents the incidence rate (incidence density) of cognitive impairments by chemotherapy status, age, tumor stage, and comorbidity. The incidence of drug-induced dementia was higher in patients receiving chemotherapy than those who did not receive chemotherapy. For example, the incidence of drug-induced dementia in patients aged 65 to 69 was 1.33 times higher in patients receiving chemotherapy than in those not receiving chemotherapy (1.64 vs. 1.23 per 10,000 person years), whereas the relative risk was 1.43 in patients aged 80 to 89 years (3.61 vs. 2.53 per 10,000 person years) between the 2 groups. However, the incidence of other types of cognitive impairments such as Alzheimer disease, vascular disorder, cognitive disorder, or other dementia was higher in patients who did not receive chemotherapy. Overall, the incidence rate of various cognitive impairments increased with advanced age and higher comorbidity scores, but fluctuated by tumor stage.

Figure 1 presents the cumulative incidence curve of the 5 types of cognitive impairments over the 16-year period by chemotherapy status. The incidence probability of drug-induced dementia was similar for chemotherapy group compared with no-chemotherapy group in the first 5 years. After 5 years, the incidence probability of drug-induced dementia became higher in the chemotherapy group than in the no-chemotherapy group, and the gap between the 2 groups became wider over time. The patterns of incidence probability were different for the other 4 types of dementia, in which the incidence probability was lower in patients receiving chemotherapy than those without chemotherapy. These patterns were similar among the matched cohorts in which the 2 groups of patients had similar probability of receiving chemotherapy (Fig. 2).

Table 3 presents the multivariate time-to-event (cognitive impairment) analysis for the hazard ratio of having various types of cognitive impairments. Patients who received chemotherapy were 8% more likely to have drug-induced dementia compared with those without chemotherapy, but that was not statistically significant after adjusting for patient and tumor characteristics. The hazard ratio of Alzheimer disease, vascular dementia, or other dementias was significantly lower in patients receiving chemotherapy except for cognitive disorder which was not significantly different between the 2 groups. Table 3 also presents the risk of cognitive impairments in association with other factors such as age, tumor stage, hormone receptor status, comorbidity, and radiation therapy. The risk of all types of cognitive impairments increased significantly with age, and higher comorbidity scores. Compared with those patients who did not receive radiation, patients with radiation therapy had a slightly lower but insignificant risk of cognitive impairments.

Table 4 presents the hazard ratio of developing various types of cognitive impairments in both entire cohort and matched cohort, stratified by the early cohort period (1991–1996) and late cohort period (1997–2002). The findings were similar between the entire cohort and the matched cohort. For example, the hazard ratio of Alzheimer disease, vascular dementia, and other dementia were lower in patients receiving chemotherapy compared with those without chemotherapy in 1997–2002 as well as in all patients. The hazard ratio of drug-induced dementia was elevated in patients in 1991–1996 that was borderline significant, but it was not significant in the later period.

Table 5 presents the risk of cognitive impairments in patients who were treated with chemotherapy compared with those who were not, stratified by the status of mood disorder. Among the entire cohort of patients who did not have a history of mood disorder, although there was a lightly elevated risk of Alzheimer disease and decreased risk of other dementias in those who received chemotherapy compared with those without chemotherapy, these were not statistically significant with wide 95% confidence intervals except for nonspecified dementia. Among those who had a history of mood disorder, patients with chemotherapy had a slightly increased but nonsignificant risk of developing drug-induced dementia (1.10, 0.86–1.40), nonsignificant risk of cognitive disorder, and significantly lower risks of Alzheimer disease, vascular dementia, or other nonspecified dementia. In the matched cohort of patients who had no history of mood disorder, there was a nonsignificant association between chemotherapy and the risk of drug-induced dementia and unspecified cognitive disorder, whereas the risk of Alzheimer disease, vascular dementia and other dementias were significantly lower in patients receiving chemotherapy. In those with a history of mood disorder, the risk of dementia was mostly lower in patients receiving chemotherapy with wider confidence intervals, likely because of small number of cases.

DISCUSSION

This study examined the incidence density, cumulative incidence, and the relative risk or hazard ratio of developing various types of cognitive impairments according to chemotherapy status in patients with breast cancer. Overall, patients who received chemotherapy were 8% more likely to have drug-induced dementia compared with those without chemotherapy, but that was not statistically significant after adjusting for patient and tumor characteristics. The risk of developing Alzheimer disease, vascular dementia, or other dementias was significantly lower in patients who received chemotherapy compared with those who did not. The risk of developing cognitive disorder was not significantly different between the 2 groups. The results were somewhat similar in the entire cohort and in the matched cohort based on the probability of receiving chemotherapy.

Although a few small-scale clinical trials documented a significant relationship between chemotherapy use and increased cognitive dysfunction in the 1990s,[19–21,25,26] it is important to realize several critical limitations in their study designs. These studies failed to have baseline neuropsychological testing before the initiation of adjuvant

TABLE 1. Comparisons of Characteristics Among Women With Breast Cancer According to the Receipt of Chemotherapy (Chemo) in Both Entire Cohort and Propensity-Matched Cohort

	Column % of the Entire Cohort			Column % of the Matched Cohort		
Characteristics	**Chemo (n = 14,057)**	**No Chemo (n = 48,508)**	***P***	**Chemo (n = 9752)**	**No Chemo (n = 9752)**	***P***
Median age (range)	76 (65–89)	71 (65–89)		72 (65–89)	72 (65–89)	
Age (yr)						
65–69	39.9	19.9	<0.001	32.4	33.4	<0.001
70–74	30.8	24.6		31.7	29.1	
75–79	19.3	25.4		22.8	21.7	
80–89	10.0	30.1		13.1	15.7	
Race/ethnicity						
Whites	85.9	88.4	<0.001	86.3	86.4	0.882
African-American	8.2	6.0		7.7	7.7	
Others	5.9	5.6		6.0	5.9	
Marital status						
Married	48.9	40.2	<0.001	46.3	45.8	0.787
Unmarried	47.7	55.7		50.1	50.5	
Unknown	3.4	4.0		3.6	3.7	
Socioeconomic status (SES)						
First quartile (high)	25.2	24.5	<0.001	25.3	23.6	0.077
Second quartile	23.6	24.8		23.5	24.5	
Third quartile	23.8	24.9		24.1	24.2	
Fourth quartile (low)	26.0	24.3		25.7	26.4	
Missing SES	1.4	1.5		1.4	1.4	
Tumor stage						
I	18.7	58.1	<0.001	26.3	25.5	0.711
II	51.6	26.5		48.2	48.3	
III	13.8	3.7		9.1	9.4	
IV	11.5	4.2		10.5	10.8	
Unstaged	4.5	7.5		5.9	6.0	
Tumor size (cm)						
<1	6.9	22.6	<0.001	9.0	8.8	0.885
1–<2	25.6	37.3		29.1	29.0	
2–<3	23.1	16.9		22.8	22.5	
3–<4	12.2	6.5		11.3	11.1	
≥4	22.6	8.8		17.7	18.0	
Missing	9.7	7.9		10.2	10.6	
No. positive lymph nodes						
0 (negative)	29.8	58.5	<0.001	39.1	38.1	0.443
1	14.3	6.4		14.0	14.9	
2–3	12.2	3.7		9.8	10.0	
4–9	13.4	2.5		8.0	8.4	
10–51	9.8	1.5		5.6	5.5	
Missing	20.6	27.4		23.5	23.2	
Tumor grade						
Well-differentiated	8.3	19.8	<0.001	10.3	10.1	0.462
Moderately differentiated	31.3	36.9		33.9	33.0	
Poorly differentiated	44.0	22.1		37.1	37.8	
Unknown/missing	16.4	21.2		18.7	19.1	
Hormone receptor status						
Positive	56.4	68.8	<0.001	60.7	60.2	0.768
Negative	25.0	8.1		18.6	18.8	
Unknown	18.6	23.1		20.7	21.0	

(*Continued*)

TABLE 1. (*Continued*)

Characteristics	Column % of the Entire Cohort			Column % of the Matched Cohort		
	Chemo (n = 14,057)	No Chemo (n = 48,508)	*P*	Chemo (n = 9752)	No Chemo (n = 9752)	*P*
Comorbidity scores						
0	71.8	66.5	<0.001	69.7	69.4	0.731
1	19.8	21.3		20.6	20.5	
≥2	8.4	12.2		9.7	10.1	
Primary surgery						
No cancer-directed surgery	6.9	5.1	<0.001	7.4	7.7	0.493
Breast conserving surgery	34.5	48.4		38.8	38.1	
Mastectomy	58.6	46.5		53.8	54.1	
Radiotherapy						
No	41.2	55.8	<0.001	48.3	49.0	0.289
Yes	58.8	44.2		51.7	51.0	
Year of diagnosis						
1991	4.5	6.9	<0.001	5.3	5.4	0.942
1992	5.0	6.9		5.9	6.0	
1993	4.4	6.6		5.1	5.1	
1994	4.6	6.6		5.1	5.2	
1995	4.9	6.7		5.5	5.7	
1996	5.1	6.6		5.5	5.3	
1997	6.1	6.8		6.4	6.6	
1998	7.1	6.5		6.8	7.2	
1999	7.8	6.6		7.1	7.1	
2000	16.1	12.7		15.2	15.2	
2001	16.9	13.4		15.8	15.4	
2002	17.5	13.6		16.3	15.6	
SEER areas						
Connecticut	9.7	11.7	<0.001	10.4	9.8	0.664
Detroit	13.7	12.7		13.5	13.5	
Hawaii	2.0	1.8		2.0	1.8	
Iowa	10.3	12.0		10.2	10.8	
New Mexico	3.2	3.5		3.3	3.2	
Seattle	7.7	8.9		7.9	7.6	
Utah	4.2	4.0		4.5	4.2	
Atlanta/rural Georgia	5.1	4.5		4.9	5.3	
Kentucky	4.0	3.3		3.9	3.8	
Louisiana	3.6	2.8		3.3	3.2	
New Jersey	9.0	5.9		8.3	8.5	
California	27.5	28.8		28.0	28.2	
Total	100.0	100.0		100.0	100.0	

chemotherapy in study participants or volunteers. Therefore, it was difficult or impossible to determine the amount of changes or differences in cognitive dysfunctions between treatment and control groups that were truly caused by adjuvant chemotherapy. In addition, all these studies had small sample sizes of treatment and control groups (about 30–40 cases in each arm), and each study also had a different approach to the neuropsychological testing. The limitations of these studies were also noticed in a review by Hurria and Lachs.[45] Therefore, these studies were considered as important hypothesis-generating studies rather than as a definitive investigation. In fact, larger prospective clinical trials of the neuropsychological sequelae of adjuvant chemotherapy in women with early stage breast cancer were reported to be underway.[46] The finding from clinical trials and observational studies may not be comparable because the 2 different study designs measured different stages of cognitive impairments. The above referenced trials tested the early decline of cognitive functions, and found a significant relationship.[19–21,25,26] Many of these early cognitive impairments (such as decline in memory and attention) may be reversible after chemotherapy stopped. The observational studies examined the late stage of cognitive impairments such as dementia[27] or all types of cognitive impairments in our study.

However, the long-term effect of chemotherapy on cognitive impairments, particularly on the clinical outcomes such as Alzheimer disease and other types of dementia, has never been documented in these clinical trials. Our study of large cohort of nationwide and population-based elderly patients with breast cancer with up to 16 years of follow-up would provide unique information on the association of chemotherapy and cognitive impairments, particularly on the various types of dementia. These patients were assumed free of any dementia at the baseline (the date of cancer diagnosis). How-

TABLE 2. Incidence Density of Cognitive Impairments by Chemotherapy Status and Other Factors in the Entire Cohort of Patients With Breast Cancer

Patient and Tumor Characteristics	Incidence Density of Cognitive Impairments (No. Cases per 1000 Person-Years), by Chemotherapy Status				
	Drug-Induced Dementia	Alzheimer's Disease	Vascular Dementia	Cognitive Disorder, NOS*	Other Dementias or Dementia, NOS*
Chemotherapy					
Age (yr)					
65–69	1.64	3.18	3.25	0.46	4.58
70–74	1.97	5.66	7.30	0.63	8.43
75–79	2.16	10.43	13.40	1.08	15.68
80–89	3.61	18.37	29.98	1.44	31.09
Tumor stage					
I	1.64	6.96	9.38	0.47	9.58
II	1.92	6.20	7.28	0.82	9.14
III	2.28	6.58	8.59	0.68	11.35
IV	4.67	2.63	7.63	0.29	8.83
Unstaged	0.93	7.27	12.44	0.62	11.18
Comorbidity scores					
0	1.72	5.86	7.13	0.67	8.27
1	2.73	7.71	11.02	0.73	12.29
≥2	3.00	7.57	12.21	0.85	17.67
Total	1.98	6.30	8.14	0.69	9.57
No chemotherapy					
Age (yr)					
65–69	1.23	4.13	5.35	0.56	6.08
70–74	1.75	8.53	11.33	0.81	12.33
75–79	1.75	14.34	19.55	1.32	21.07
80–89	2.53	24.56	37.88	1.48	37.54
Tumor stage					
I	1.62	11.06	14.82	0.97	16.13
II	2.01	14.80	22.14	1.08	22.67
III	2.15	18.72	35.77	1.44	32.58
IV	5.32	16.34	33.51	2.66	35.50
Unstaged	2.22	15.75	22.49	1.17	20.59
Comorbidity scores					
0	1.41	12.01	15.46	0.95	16.38
1	2.46	13.72	21.96	1.17	22.42
≥2	3.83	14.71	29.67	1.51	30.16
Total	1.81	12.55	17.82	1.04	18.63

*NOS indicates not otherwise specified.

ever, the association between chemotherapy use and the risk of developing Alzheimer disease, vascular dementia, or other dementias was no longer significant after controlling for mood disorders. This finding did not support the findings from previous small-scale clinical trials. The following reasons might have explained the discrepancy. First, those small scale trials only tested the early stage cognitive impairments (such as decline in memory or attention), while our study examined some late-stage cognitive impairments (such as Alzheimer disease). Second, these clinical trials had a short follow-up time, and were unable to observe the long-term outcomes such as the manifestation of memory loss or a typical dementia. Third, the early stage cognitive impairments may get improved or recovered after patients completed or stopped chemotherapy, so that they may not progress to the late-stages. This could be one of reasons why there was no significantly increased risk of dementia in association with the use of chemotherapy. Furthermore, in patients with a history of mood disorder, the risk of Alzheimer disease, cognitive disorder and other dementias was lower in patients who received chemotherapy than those without such a therapy. There may be possibility that patients with mood disorders could have prevented them from receiving chemotherapy in the first place by physicians in charge or medical oncologists.

As referenced in the introduction, a recent study looked at the relationship between chemotherapy and the risk of all dementias combined.[27] Their findings and conclusion were that the risk of dementia was more common in patients who did not receive chemotherapy in the first few years, and in the longer term the risk of dementia became higher in patients receiving chemotherapy (hazard ratio = 1.20, 95% CI 1.08–1.33).[27] Although this project by Heck et al only studied all dementias combined and did not specify any specific type of dementia, the finding and conclusion were similar to what was found in our study on the risk of drug-induced dementia.

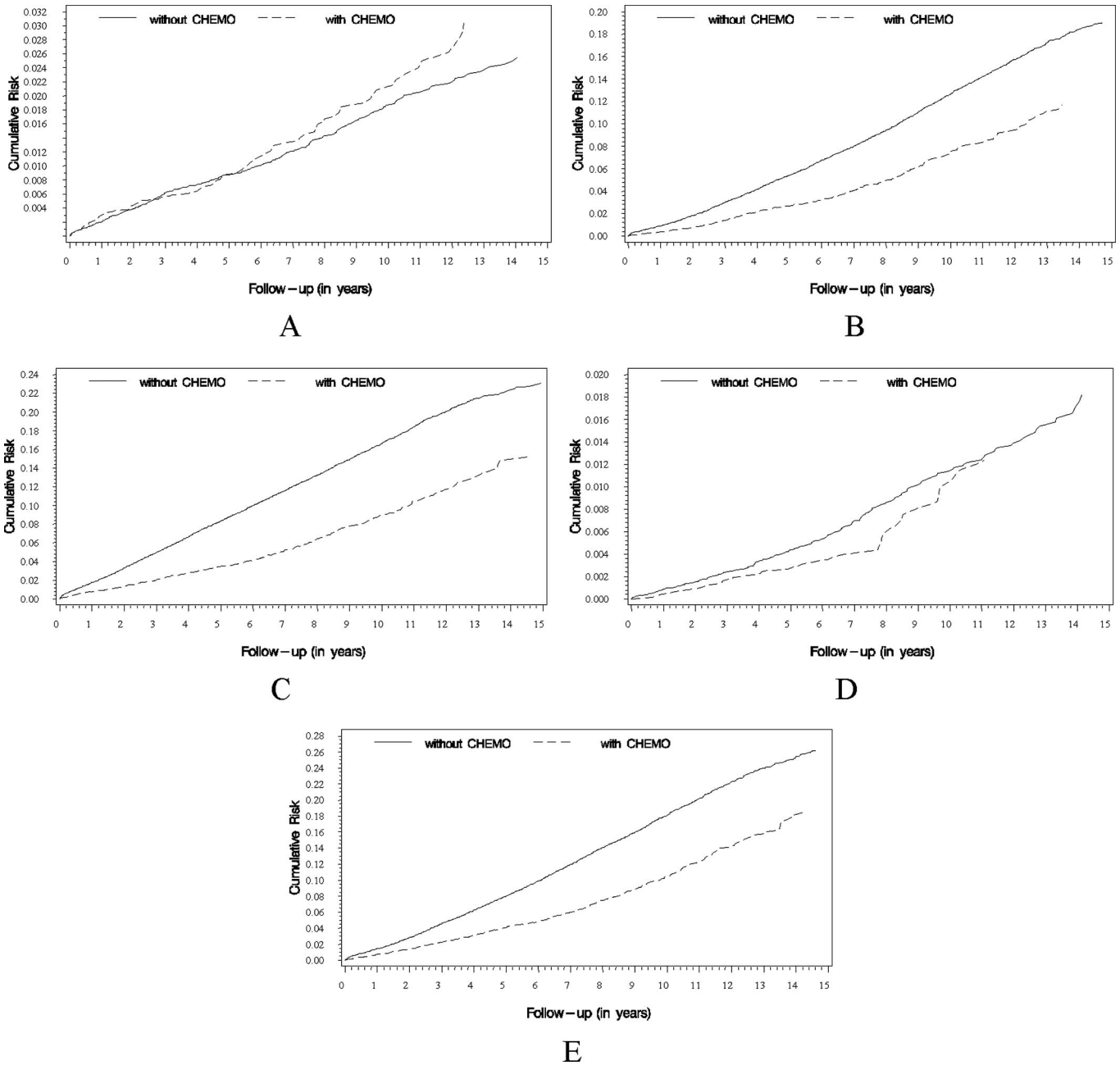

FIGURE 1. Cumulative incidence of the 5 types of dementia for the entire cohort. A, drug-induced dementia; B, Alzheimer disease; C, vascular dementia; D, other disorder; E, nonspecified dementia.

As shown in Figure 1, the cumulative incidence was higher in patients who did not receive chemotherapy in the first 5 years, but was higher in those who received chemotherapy after 5 years. The gap between 2 groups seemed to be getting wider over time. This finding may potentially be confounded by some unmeasured factors at baseline that might have influenced or affected patients or physicians to choose chemotherapy. This explanation was at least partially supported by the finding that there was no difference in the cumulative incidence of drug-induced dementia between the 2 groups from the matched cohort (Fig. 2).

This study had a number of strengths. First, our study population covered truly community-based Medicare beneficiaries aged 65 or older. This was particularly important because only a small proportion of elderly patients were ever enrolled in clinical trials. Also, patients tested in the trials were mostly motivated volunteers and had relatively less comorbid conditions. Thus, our study populations were more representative of the target population. Second, a unique feature of our study was that we only included those patients who were free of any cognitive impairment at the time of cancer diagnosis, thus leading the results toward cause-effect temporal relationship. Furthermore, the analysis on cognitive impairments was stratified by the status of mood disorder which was shown to be significantly associated with cognitive impairments. Third, the Medicare claims data covered all medical services provided, includ-

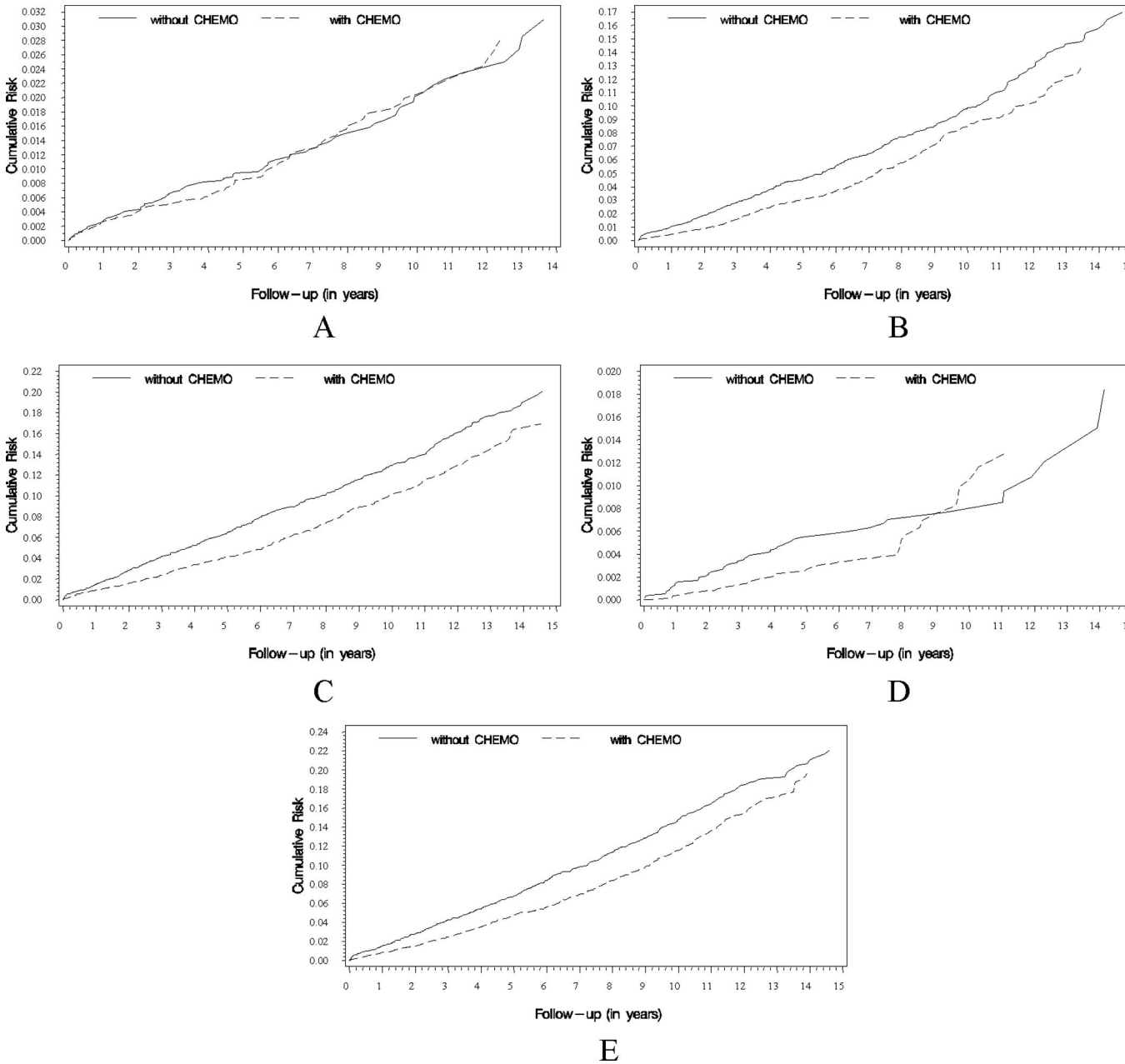

FIGURE 2. Cumulative incidence of the 5 types of dementia for the matched cohort. A, drug-induced dementia; B, Alzheimer disease; C, vascular dementia; D, other disorder; E, nonspecified dementia.

ing inpatient hospitalization, outpatient clinics and physician office visits, regardless of where the patients seek their care across the United States, thus ensuring more completeness of the information on treatment and associated medical conditions. Fourth, a large retrospective cohort of patients had been followed up for up to 16 years, allowing for more adequate assessment on patient's dementia status by their physicians. Fifth, Medicare claims data with the date of diagnosis and medical service after cancer diagnosis and therapy allowed the time to event (cognitive impairments) analysis, thus maximizing the information on the estimate of the association between chemotherapy and the occurrence of dementia. Finally, the SEER-Medicare data not only provided well-validated information on tumor characteristics (stage and histologic type) at diagnosis, but also allowed the examination of socioeconomic factor at the census tract level and controlled for comorbidity scores in the analysis. Because some comorbid conditions might be associated with the risk of dementia or other cognitive impairments, controlling for comorbidity was helpful in minimizing residual confounding when addressing this association.

It was important to note several important limitations of this study. First, our study outcomes only included more serious and late-stage cognitive impairments (such as Alzheimer disease and other types of dementia) that are based on the ICD-9 diagnosis codes in Medicare claims data. The claims data did not allow assessment of the early stage or process (such as decline in memory or attention) of cognitive impairments and therefore might not be comparable to

TABLE 3. Relative Risk (Hazard Ratio) of Cognitive Impairments in the Entire Cohort of Patients Receiving Chemotherapy Compared to Those Not, Controlling for Other Factors

	Hazard Ratio* (95% CI) of Having Cognitive Impairments				
Characteristics	**Drug-Induced Dementia**	**Alzheimer's Disease**	**Vascular Dementia**	**Cognitive Disorder, NOS**	**Other Dementias or Dementia NOS***
Chemotherapy					
No chemotherapy	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Chemotherapy	1.08 (0.85–1.37)	0.76 (0.67–0.85)	0.72 (0.65–0.80)	0.85 (0.60–1.21)	0.77 (0.70–0.85)
Age (yr)					
65–69	1.00	1.00	1.00	1.00	1.00
70–74	1.29 (1.04–1.60)	2.01 (1.78–2.26)	2.10 (1.89–2.34)	1.40 (1.00–1.97)	1.96 (1.78–2.17)
75–79	1.23 (0.98–1.54)	3.44 (3.07–3.85)	3.51 (3.17–3.88)	2.26 (1.63–3.13)	3.30 (3.00–3.63)
80–89	1.60 (1.27–2.03)	5.71 (5.09–6.41)	6.04 (5.45–6.68)	2.36 (1.67–3.32)	5.48 (4.98–6.03)
Comorbidity scores					
0	1.00	1.00	1.00	1.00	1.00
1	1.62 (1.36–1.93)	1.09 (1.01–1.18)	1.32 (1.24–1.40)	1.15 (0.89–1.48)	1.27 (1.19–1.35)
≥2	2.27 (1.83–2.83)	1.11 (0.99–1.23)	1.62 (1.50–1.76)	1.44 (1.03–2.02)	1.64 (1.52–1.77)
Radiotherapy					
No	1.00	1.00	1.00	1.00	1.00
Yes	0.89 (0.73–1.09)	0.75 (0.69–0.82)	0.69 (0.64–0.74)	1.00 (0.75–1.33)	0.72 (0.67–0.77)

*Hazard ratio was adjusted for age, ethnicity, marital status, tumor stage, tumor grade, hormone receptor status, comorbidity, radiation therapy, socioeconomic status, year of diagnosis, and SEER areas. The number of cases originally categorized as Amnestic disorder was small, therefore those cases were combined with category "Other dementia/NOS." ref denotes reference group.

TABLE 4. Hazard Ratio of Cognitive Impairments in Both Entire Cohort and Matched Cohort of Patients Receiving Chemotherapy Compared to Those Not, Stratified by Year of Diagnosis

	Hazard Ratio* (95% CI) of Having Cognitive Impairments				
Characteristics	**Drug-Induced Dementia**	**Alzheimer's Disease**	**Vascular Dementia**	**Cognitive Disorder, NOS**	**Other Dementias or Dementia NOS***
Entire cohort 1991–1996					
No chemotherapy	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Chemotherapy	1.37 (0.99–1.91)	0.89 (0.76–1.04)	0.82 (0.72–0.94)	0.98 (0.61–1.57)	0.91 (0.80–1.04)
Entire cohort 1997–2002					
No chemotherapy	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Chemotherapy	0.86 (0.61–1.21)	0.65 (0.55–0.78)	0.61 (0.52–0.72)	0.70 (0.42–1.18)	0.67 (0.58–0.77)
Entire cohort all (1991–2002)					
No chemotherapy	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Chemotherapy	1.08 (0.85–1.37)	0.76 (0.67–0.85)	0.72 (0.65–0.80)	0.85 (0.60–1.21)	0.77 (0.70–0.85)
Matched cohort 1991–1996					
No chemotherapy	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Chemotherapy	1.03 (0.68–1.55)	0.91 (0.75–1.10)	0.86 (0.73–1.00)	1.30 (0.71–2.38)	0.94 (0.80–1.10)
Matched cohort 1997–2002					
No chemotherapy	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Chemotherapy	0.91 (0.59–1.38)	0.63 (0.51–0.78)	0.59 (0.49–0.72)	0.63 (0.32–1.23)	0.62 (0.52–0.73)
Matched cohort all (1991–2002)					
No chemotherapy	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Chemotherapy	0.93 (0.69–1.25)	0.76 (0.66–0.87)	0.72 (0.64–0.82)	0.90 (0.59–1.39)	0.76 (0.68–0.85)

*Hazard ratio was adjusted for age, ethnicity, marital status, tumor stage, tumor grade, hormone receptor status, comorbidity, radiation therapy, socioeconomic status, year of diagnosis, and SEER areas. The number of cases originally categorized as Amnestic disorder was small, therefore those cases were combined with category "Other dementia/NOS."

less severe or early stage of cognitive impairments that are often identified in previous clinical trials.[19–21,25,26] Even though we adjusted for some measured confounding factors and used the matched cohort analysis, there could have been unmeasured factors that were associated with subtle differences in patent's cognitive status, which could have influenced physicians to prescribe chemotherapy or not to do so. The potential selection bias could not be totally ruled out in this study, which might have explained why the risk of several types of dementia (Alzheimer disease, vascular dementia, or other dementias) was even slightly lower in patients

TABLE 5. Hazard Ratio of Developing Cognitive Impairments in Entire Cohort and Matched Cohort of Patients With Breast Cancer Who Received Chemotherapy Compared With Those Without Receiving Chemotherapy, Stratified by the Status of Mood Disorder

Type of Cognitive Impairments	Hazard Ratio (95% CI)* of Having Cognitive Impairments in Patients Receiving Chemotherapy Compared With Those Who Did Not, by Status of Mood Disorder Prior to Cancer Diagnosis	
	Had Mood Disorder	No Mood Disorder
Entire cohort	(n = 2387)	(n = 60,178)
Drug-induced dementia	1.10 (0.86–1.40)	0.91 (0.38–2.17)
Alzheimer's disease	0.74 (0.65–0.83)	1.11 (0.71–1.74)
Vascular dementia	0.73 (0.66–0.81)	0.70 (0.48–1.01)
Cognitive disorder, NOS	0.92 (0.64–1.32)	0.51 (0.14–1.89)
Other dementias or dementia NOS	0.80 (0.72–0.88)	0.59 (0.40–0.89)
Matched cohort	(n = 731)	(n = 18,773)
Drug-induced dementia	0.65 (0.16–2.74)	0.96 (0.71–1.30)
Alzheimer's disease	0.94 (0.48–1.83)	0.75 (0.65–0.86)
Vascular dementia	0.70 (0.43–1.15)	0.73 (0.65–0.83)
Cognitive disorder, NOS	6.90 (0.37–130.0)	0.99 (0.62–1.58)
Other dementias or dementia NOS	0.51 (0.30–0.87)	0.78 (0.69–0.88)

*Hazard ratio was adjusted for age, ethnicity, marital status, tumor stage, tumor grade, hormone receptor status, comorbidity, radiation therapy, socioeconomic status, year of diagnosis, and SEER areas.

who received chemotherapy compared with those who did not. In addition, Medicare claims had limited information on the dosage and intensity of chemotherapy that could have affected the occurrence and severity of cognitive impairments. We relied on the common procedure codes that specified the standard dose for each chemotherapy agents, but in practice physician might have modified the chemotherapy doses according to each individual patient's characteristics. Also, this study did not examine the types of chemotherapy used and the number of cycles administered, and their potential effects on the outcomes. It was also unknown how the study outcomes on cognitive impairments might be affected by brain metastasis in patients with breast cancer. Furthermore, although Medicare claims on overall chemotherapy administration were externally well validated, the validity of claims on cognitive impairments had not been well evaluated. Finally, if patients had private medical service but their services or claims were not filed to the Medicare for reimbursement from the private medical providers, although rare, these diagnosis and procedure information might be missed in the study using Medicare claims, thus leading to bias toward the exposure-outcomes association.

In conclusion, there was no significant association between chemotherapy and the risk of developing drug-induced dementia and unspecified cognitive disorders. The risk of developing Alzheimer disease, vascular dementia, or other dementias was significantly lower in patients receiving chemotherapy. Although it is important to evaluate patient's cognitive conditions at the time of chemotherapy, this study with long-term follow-up did not support the findings that chemotherapy was associated with an increased risk of late stage cognitive impairments.

ACKNOWLEDGMENTS

The authors thank the efforts of the NCI, CMS, IMS, and the SEER registries in the creation of this database.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet*. 1998;352:930–942.
2. Cole BF, Gelber RD, Gelber S, et al. Polychemotherapy for early breast cancer: an overview of the randomized clinical trials with quality-adjusted survival analysis. *Lancet*. 2001;358:277–286.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687–1717.
4. Du XL, Goodwin JS. Increase of chemotherapy use in older women with breast carcinoma from 1991 to 1996. *Cancer*. 2001;92:730–737.
5. Mariotto A, Feuer EJ, Harlan LC, et al. Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975–1999. *J Natl Cancer Inst*. 2002;94:1626–1634.
6. Hassett MJ, Hughes ME, Niland JC, et al. Chemotherapy use for hormone receptor-positive, lymph node-negative breast cancer. *J Clin Oncol*. 2008;26:5553–5560.
7. National Institutes of Health Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1–3, 2000. *J Natl Cancer Inst*. 2001;93:979–989.
8. Silberfarb PM, Philibert D, Levine PM. Psychosocial aspects of neoplastic disease: II. Affective and cognitive effects of chemotherapy in cancer patients. *Am J Psychiatry*. 1980;137:597–601.
9. Oxman TE, Silberfarb PM. Serial cognitive testing in cancer patients receiving chemotherapy. *Am J Psychiatry*. 1980;137:1263–1265.
10. Devlen J, Maguire P, Phillips P, et al. Psychological problems associated with diagnosis and treatment of lymphomas. II: prospective study. *Br Med J*. 1987;295:955–957.
11. Parth P, Dunlap WP, Kennedy RS, et al. Motor and cognitive testing of bone marrow transplant patients after chemoradiotherapy. *Percept Mot Skills*. 1989;68:1227–1241.
12. Copeland DR, Moore BD III, Francis DJ, et al. Neuropsy-chologic effects of chemotherapy on children with cancer: a longitudinal study. *J Clin Oncol*. 1996;14:2826–2835.
13. Waber DP, Tarbell NJ, Fairclough D, et al. Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: cranial radiation requires an accomplice. *J Clin Oncol*. 1995;13:2490–2496.
14. Ahles TA, Silberfarb PM, Rundle AC, et al. Quality of life in patients with limited small-cell carcinoma of the lung receiving chemotherapy with or without radiation therapy, for Cancer and Leukemia Group B. *Psychother Psychosom*. 1994;62:193–199.
15. Wieneke MH, Dienst ER. Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. *Psycho Oncol*. 1995;4:61–66.
16. Meyers CA, Byrne KS, Komaki R. Cognitive deficits in patients with small cell lung cancer before and after chemotherapy. *Lung Cancer*. 1995;12:231–235.
17. Schwartz CL. Late effects of treatment in long-term survivors of cancer. *Cancer Treat Rev*. 1995;21:355–366.
18. Shapiro CL, Recht A. Drug therapy: side effects of adjuvant treatment of breast cancer. *N Engl J Med*. 2001;344:1997–2008.
19. van Dam FS, Schagen SB, Muller MJ, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *J Natl Cancer Inst*. 1998;90:210–218.
20. Schagen SB, van Dam FS, Muller MJ, et al. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer*. 1999;85:640–650.
21. Schagen SB, Hamburger HL, Muller MJ, et al. Neurophysiological evaluation of late effects of adjuvant high-dose chemotherapy on cognitive function. *J Neurooncol*. 2001;51:159–165.
22. Schagen SB, Muller MJ, Boogerd W, et al. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. *J Natl Cancer Inst*. 2006;98:1742–1745.
23. Schagen SB, van Dam FS. Does cognitive impairment after chemotherapy for breast cancer improve over time or does practice make perfect? *J Clin Oncol*. 2006;24:5170–5171.
24. Kreukels BP, van Dam FS, Ridderinkhof KR, et al. Persistent neurocognitive problems after adjuvant chemotherapy for breast cancer. *Clin Breast Cancer*. 2008;8:80–87.
25. Brezden CB, Phillips KA, Abdolell M, et al. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol*. 2000;18:2695–2701.
26. Wefel JS, Lenzi R, Theriault RL, et al. The cognitive sequelae of standard-

dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer*. 2004;100:2292–2299.

27. 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.
28. Hurria A, Rosen C, Hudis C, et al. Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: a pilot prospective longitudinal study. *J Am Geriatr Soc*. 2006;54:925–931.
29. National Cancer Institute. Surveillance epidemiology and end results. Available at: http://seer.cancer.gov/index.html. Accessed October 20, 2008.
30. Warren JL, Klabunde CN, Schrag D, et al. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40(suppl 8):IV3–IV18.
31. Parsons LS. Reducing bias in a propensity score matching-pair sample using greedy matching techniques. Available at: http://www2.sas.com/proceedings/sugi26/p214–26.pdf. Accessed November 19, 2008.
32. Du XL, Goodwin JS. Patterns of use of chemotherapy for breast cancer in older women: findings from Medicare claims data. *J Clin Oncol*. 2001;19:1455–1461.
33. Du XL, Key CR, Dickie L, et al. External validation of Medicare claims for breast cancer chemotherapy compared with medical chart reviews. *Med Care*. 2006;44:124–131.
34. US Public Health Services. *International Classification of Diseases, 9th Revision, Clinical Modification*. 5th ed. Los Angeles, CA: Practice Management Information Corporation; 1996.
35. American Medical Association. *Physicians' Current Procedural Terminology-CPT 2000*. Chicago, IL: American Medical Association; 2000.
36. Health Care Financing Administration. *HCFA Common Procedure Coding System: National Level II Medicare Codes*. Los Angeles, CA: Practice Management Information Corporation; 2000.
37. National Cancer Institute. SEER-Medicare: Calculation of Comorbidity Weights. Available at: http://healthservices.cancer.gov/seermedicare/program/comorbidity.html. Accessed July 23, 2007.
38. Klabunde CN, Potosky AL, Legler JM, et al. Development of a comorbidity index using physician claims data. *J Clin Epidemiol*. 2000;53:1258–1267.
39. Du XL, et al. Variation in modes of chemotherapy administration for breast carcinoma and association with hospitalization for chemotherapy-related toxicity. *Cancer*. 2005;104:913–924.
40. Charlson ME, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
41. Romano PS, et al. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol*. 1993;46:1075–1079.
42. Deyo RA, Cherkin DC, Ciol MA, et al. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613–619.
43. Penman AD, Johnson WD. A SAS program for calculating cumulative incidence of events (with confidence limits) and number at risk at specified time intervals with partially censored data. *Comput Methods Programs Biomed*. 2008;89:50–55.
44. Allison PD. *Survival Analysis Using the SAS System: A Practical Guide*. Cary, NC: SAS Institute Inc.; 1995.
45. Hurria A, Lachs M. Is cognitive dysfunction a complication of adjuvant chemotherapy in the older patient with breast cancer? *Breast Cancer Res Treat*. 2007;103:259–268.
46. Ganz PA. Cognitive dysfunction following adjuvant treatment of breast cancer: a new dose-limiting toxic effect? *J Natl Cancer Inst*. 1998;90:182–183.