

Association between chemotherapy and cognitive impairments in a large cohort of patients with colorectal cancer

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Abstract. No population-based study has been conducted on the relationship between chemotherapy and the risk of cognitive impairments in patients with colorectal cancer. This study aimed to determine this association in a large population-based cohort of patients. We studied 72,374 men and women who were diagnosed with stages I-III colorectal 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 baseline with up to 17 years of follow-up and also studied 15,921 matched cohorts based on the propensity of receiving chemotherapy. The cumulative incidence of drug-induced dementia at 5 years was 16.2 cases per 1,000 persons for the chemotherapy group and 12.4 cases per 1,000 persons for the no chemotherapy group. Overall, patients who received chemotherapy were 24% significantly more likely to develop drug-induced dementia compared to those without chemotherapy after adjusting for patient and tumor characteristics (hazard ratio 1.24, 95% confidence interval 1.05-1.47). The significantly increased risk was only observed in those without mood disorder who received chemotherapy in the entire cohort (1.26, 1.06-1.50) and in the matched cohort (1.29, 1.04-1.59). The risk of developing Alzheimer's disease, vascular dementia or other dementias was significantly lower in patients receiving chemotherapy compared to those without chemotherapy regardless of mood disorder status. In conclusion, there was a significant association between chemotherapy and the risk of developing drug-induced dementia in patients with colorectal cancer without mood disorder, but chemotherapy was associated with a decreased risk of other dementias.

Introduction

Chemotherapy has been documented to be efficacious in treating men and women with stage III colon cancer (1-5) and the clinical guidelines are clear about recommending adjuvant chemotherapy for these patients after resection (1,5). For patients with stages II-III rectal cancer, the combined-modality of adjuvant chemotherapy and radiation therapy is currently the standard of care (1,5). Although chemotherapy is not well documented in randomized trials for those with stage I or II colon cancer (6-11), a substantial number of patients with stage II colon cancer received chemotherapy (12,13). What has not been well studied is the potential association between chemotherapy utilization and the risk of cognitive impairments in patients with cancer treated with chemotherapy. There have been some anecdotal reports since the 1980s, indicating that patients treated with chemotherapy complained of changes in their memory, attention, concentration, and language skills primarily in those with cancer (14-23). The first study that examined this relationship within the context of a randomized trial was reported by van Dam and colleagues in 1998 for patients with breast cancer (24). In the treatment group, they administered four cycles of combination chemotherapy agents (fluorouracil, doxorubicin and cyclophosphamide); and a fifth course of high-dose combination chemotherapy (cyclophosphamide and carboplatin) (24). The subsequent small-scale studies seemed to support the original findings (25-32). However, minor cognitive impairments (such as minor decrease in memory, attention, concentration and language skills) may be reversible after a short time use of chemotherapy, even if there were true causal relationships. No clinical trials have been conducted to determine the association between chemotherapy and long-term follow-up of outcomes such as dementia, which are unlikely to be reversed.

There have been four population-based studies examining a long-term relationship between chemotherapy and dementia (33-36) and one of these studies examined the 5 types of cognitive impairments (36), all of which were conducted in breast cancer patients. No nationwide large population-based study has been conducted on this research question in patients with colorectal cancer. Because similar chemotherapy agents such as fluorouracil are commonly used in patients with colorectal cancer as well as in patients with breast cancer, it is reasonable to posit that, if chemotherapy use increased the risk

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of cognitive impairments in patients with breast cancer, this relationship will likely be observed in those with colorectal cancer who received similar chemotherapy agents. Therefore, this study aimed to primarily determine the long-term risk of drug-induced dementia associated with chemotherapy use and also explore if the use of chemotherapy was associated with the risks of other cognitive impairments, including Alzheimer's disease, in a large population-based cohort of patients with colorectal cancer in the US with up to 17 years of follow-up. In this study, only those patients who were free of any cognitive impairment at baseline were included. Moreover, additional matched-cohort analysis according to the propensity of receiving chemotherapy was conducted to verify the study findings and to assess the potential impact of selection bias that might have affected the study findings. Our hypothesis was that there were significant differences in the occurrence of developing cognitive impairments in men and women diagnosed with colorectal cancer who received chemotherapy compared to those who did not use chemotherapy.

Patients and methods

Data sources and study population. The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 16 cancer registries and Medicare linked databases were used for this analysis (37,38). The Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston approved this study.

The study population consisted of 120,111 patients who were diagnosed with colorectal cancer as the only primary tumor at age ≥ 65 years from 1991 through 2002. Cases from Atlanta and rural Georgia were combined due to small numbers in the same state. We excluded 35,475 subjects who did not have full coverage of Medicare Parts A and B or were enrolled with Health Maintenance Organizations from the year of diagnosis to the last follow-up (December 2006 or date of death). 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 at the time of cancer diagnosis. By doing so, we excluded 4,078 cases with preexisting cognitive impairments, 5,129 patients aged ≥ 90 and 3,073 cases who received first chemotherapy after 12 months of diagnosis, leaving 72,374 subjects for the final analysis.

Matched cohort. In order to minimize selection bias due to 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. The propensity of receiving chemotherapy was created through the logistic regression model based on the following patient and tumor characteristics: age, sex, ethnicity, marital status, tumor stage, tumor grade, tumor size, number of positive lymph nodes, comorbidity, surgery, radiotherapy, socioeconomic status, cancer type, year of diagnosis and SEER areas. The matching through the 5-1 digit propensity of receiving chemotherapy was performed using the greedy matching algorithm by

Parsons (39). A total of 15,921 patients receiving chemotherapy were matched with 15,921 patients who did not receive chemotherapy.

Chemotherapy. The methods of identifying chemotherapy use through the Medicare claims was discussed elsewhere (40) and the validity of Medicare claims for chemotherapy have been reasonably well confirmed (41-48).

Cognitive impairments and mood disorders. Cognitive impairment was defined if there were at least two claims in all Medicare claim files (including inpatient, outpatient and physician claims) that were 30 days apart for each of the following diagnoses (with ICD-9-CM codes) (46) after chemotherapy use: unspecified cognitive disorder (294.9), amnestic disorder (294.0), Alzheimer's disease (331.0), vascular dementia (290.x), unspecified dementia (294.8) or drug-induced dementia and psychoses (292.x).

Mood disorder was defined if there were at least two claims that were 30 days apart for each of the following diagnoses (46) before or after chemotherapy use: anxiety state, unspecified (300.0); anxiety depression (300.4); unspecified depressive disorder, (311.x); alteration of consciousness (780.9); and other depressions (296.2, 296.3, 296.5-296.7, 298.0, 301.10, 301.12, 301.13, 309.0, 309.1).

Other variables. Comorbidity was ascertained from Medicare claims data through diagnoses or procedures that were made between 1 year prior to and 1 month after the diagnosis of colorectal cancer using the previously validated comorbidity index (49-51) and SAS macro program (52). The percent of persons living below the poverty line at the census tract level from the 1990 census for cases in 1991-1999 and from the 2000 census for cases in 2000-2002 was used to define the socioeconomic status (SES). These percentages were then classified into quartiles.

Analyses. The χ^2 statistic (at a significance level of 0.05) was used to compare baseline characteristics between patients 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 (53). The time to event (cognitive impairment) analysis was conducted using the Cox proportional hazard regression model available in SAS (54).

Results

Table I presents the distribution of baseline characteristics among the entire cohort of patients with colorectal cancer according to chemotherapy status and also presents the comparisons of the matched cohort based on propensity score of receiving chemotherapy. In the entire cohort, a significantly

Table I. Comparisons of characteristics among women with colon cancer according to the receipt of chemotherapy (chemo) in both entire cohort and propensity-matched cohort.

Characteristics	Column % of the entire cohort			Column % of the matched cohort		
	Chemo (n=23,484)	No chemo (n=48,890)	P-value	Chemo (n=15,921)	No chemo (n=15,921)	P-value
Median age (range)	73 (65-89)	78 (65-89)		75 (65-89)	75 (65-89)	
Age (years)						
65-69	28.1	14.4	<0.001	21.4	21.4	0.817
70-74	30.7	19.8		27.5	27.4	
75-79	24.7	24.2		27.9	27.8	
80-84	12.8	24.1		17.7	17.6	
85-89	3.7	17.4		5.4	5.8	
Gender						
Male	48.6	43.9	<0.001	47.2	47.1	0.893
Female	51.4	56.1		52.8	52.9	
Race/ethnicity						
Caucasians	85.1	84.3	<0.001	84.4	84.1	0.725
African Americans	6.7	8.1		7.5	7.8	
Others	8.2	7.6		8.1	8.1	
Marital status						
Married	59.3	45.2	<0.001	53.7	53.3	0.712
Unmarried	37.9	50.5		42.9	43.1	
Unknown	2.8	4.3		3.4	3.5	
Socioeconomic status (SES)						
First quartile (high)	26.8	23.6	<0.001	24.7	24.5	0.789
Second quartile	25.2	24.3		24.8	24.6	
Third quartile	24	24.9		24.9	24.8	
Fourth quartile (low)	22.5	25.5		24.1	24.5	
Missing SES	1.4	1.7		1.5	1.6	
Tumor stage						
I	5.5	33.0	<0.001	8.2	7.8	0.676
II	22.9	29.4		29.7	29.8	
III	41.0	12.9		29.2	28.9	
IV	25.7	15.8		26.7	27.1	
Unstaged	4.9	8.8		6.2	6.4	
Tumor size (cm)						
<1	0.5	2.9	<0.001	0.7	0.7	0.959
1-<2	2.1	4.1		2.3	2.2	
2-<3	7.6	8.6		7.5	7.4	
3-<4	14.6	12.9		13.7	13.8	
≥4	56.1	41.0		53.7	53.9	
Missing	19.0	30.6		22.1	22.0	
N of positive lymph nodes						
0 (negative)	27.1	50.6	<0.001	35.6	35.1	0.889
1	14.9	5.4		12.1	12	
2-3	16.7	5.4		12.2	12.1	
4-9	15.8	5.0		11.4	11.5	
10-51	6.7	2.6		5.5	5.7	
Missing	18.8	31.1		23.2	23.5	

Table I. Continued.

Characteristics	Column % of the entire cohort			Column % of the matched cohort		
	Chemo (n=23,484)	No chemo (n=48,890)	P-value	Chemo (n=15,921)	No chemo (n=15,921)	P-value
Tumor grade						
Well-differentiated	5.5	9.9	<0.001	6.2	6.0	0.815
Moderately-differentiated	61.5	56.4		60.1	60.1	
Poorly-differentiated	24.6	16.2		22.8	23.0	
Unknown/missing	8.4	17.5		10.8	10.9	
Comorbidity scores						
0	61.5	51.0	<0.001	57.6	57.2	0.799
1	25.4	26.7		26.3	26.6	
≥2	12.1	22.3		16.1	16.2	
Primary surgery (resection)						
No	11.3	17.6	<0.001	14.5	15.0	0.200
Yes	88.7	82.4		85.5	85.0	
Radiotherapy						
No	71.7	88.6	<0.001	79.6	79.5	0.911
Yes	28.3	11.4		20.4	20.5	
Year of diagnosis						
1991	7.2	7.2	<0.001	7.4	7.6	0.945
1992	7.3	7.1		7.2	7.4	
1993	6.9	6.8		6.6	6.9	
1994	6.6	6.7		6.6	6.6	
1995	7.0	6.5		6.7	6.8	
1996	6.6	6.3		6.6	6.2	
1997	6.8	6.3		6.8	6.8	
1998	7.0	6.4		6.5	6.6	
1999	6.0	6.4		6.1	5.9	
2000	10.2	14.2		12.0	11.9	
2001	14.0	12.8		13.5	13.8	
2002	14.4	13.3		13.8	13.5	
SEER areas						
Connecticut	12.2	11.8	<0.001	11.5	12.1	0.899
Detroit	14.0	12.8		13.6	13.2	
Hawaii	2.1	2.0		2.0	1.9	
Iowa	13.0	13.6		12.9	12.7	
New Mexico	2.9	3.4		3.2	3.2	
Seattle	7.4	7.5		7.2	7	
Utah	3.1	3.5		3.3	3.2	
Atlanta/rural Georgia	4.7	4.4		4.6	4.8	
Kentucky	3.6	3.8		3.8	3.9	
Louisiana	2.8	2.9		2.8	2.9	
New Jersey	7.5	7.1		7.4	7.2	
California	26.7	27.2		27.7	27.8	
Cancer type						
Colon cancer	69.9	77.1	<0.001	74.6	74.3	0.550
Rectal cancer	30.1	22.9		25.4	25.7	
Total	100.0	100.0		100.0	100.0	

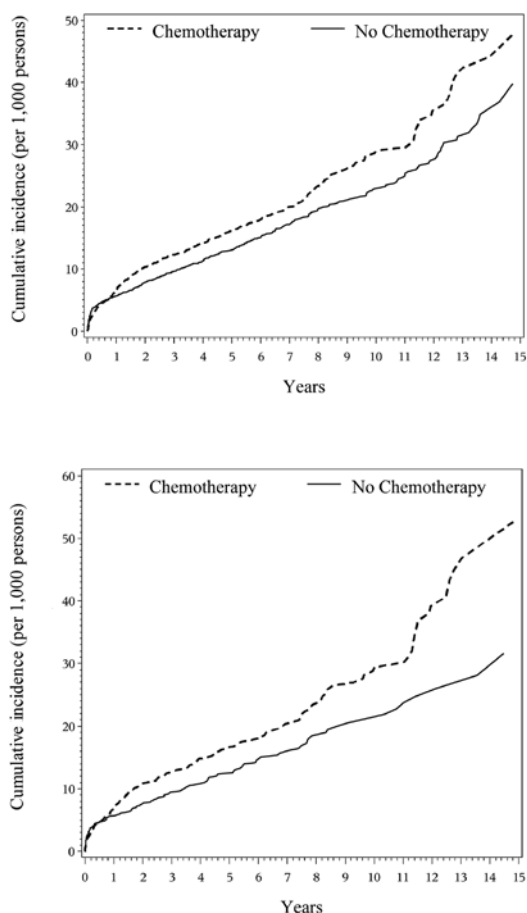


Figure 1. Cumulative incidence of drug-induced dementia in patients with colorectal cancer, by chemotherapy status. Top, entire cohort; bottom, matched cohort.

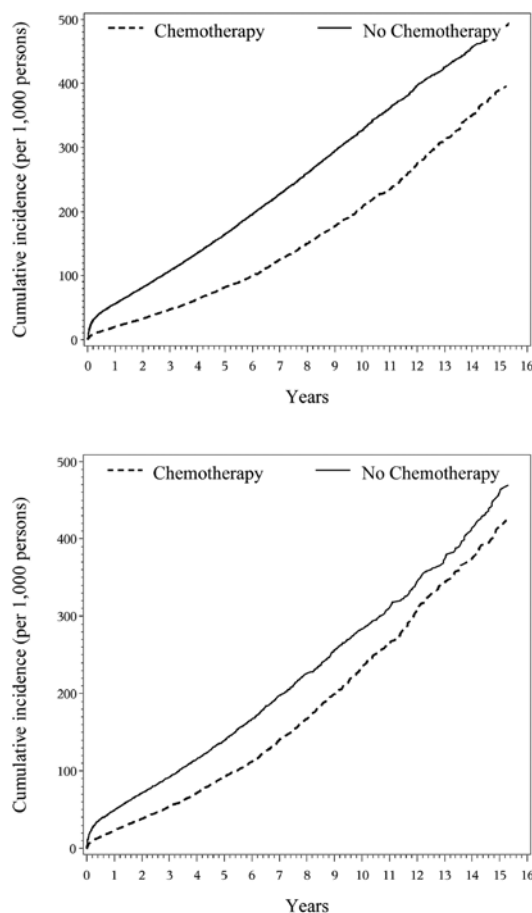


Figure 2. Cumulative incidence of any dementia in patients with colorectal cancer, by chemotherapy status. Top, entire cohort; bottom, matched cohort.

higher proportion of younger patients and married people received chemotherapy. A slightly higher percentage of women and Caucasians received chemotherapy. The higher percentage of not receiving chemotherapy was related to lower socioeconomic status, earlier tumor stage, smaller tumor size, fewer positive lymph nodes, low grade tumors and higher comorbidity scores. A higher proportion of patients who had resection and radiation therapy also 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 were no significant differences between these two groups in terms of all baseline characteristics.

Table II presents the incidence density of cognitive impairments by chemotherapy status, age, gender, tumor stage and comorbidity. The incidence density of drug-induced dementia was higher in patients receiving chemotherapy than those who did not receive chemotherapy in all strata of age, sex, stage and comorbidity score. For example, the incidence of drug-induced dementia in patients aged 65-69 was 1.84 times higher in patients receiving chemotherapy than in those not receiving chemotherapy (3.33 versus 1.81 per 10,000 person-years), whereas the relative risk was 1.42 in patients aged 80-84 years (5.15 versus 3.63 per 10,000 person-years) between the two groups. However, the incidence of other types of cognitive impairments such as Alzheimer's disease, vascular disorder,

cognitive disorder or other dementia appeared to be 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 was relatively similar across gender and tumor stage.

Fig. 1 presents the cumulative incidence curve of drug-induced dementia over the 15-year period by chemotherapy status. The probability of drug-induced dementia was similar for chemotherapy group compared to no chemotherapy group in the first year. After the first year, the incidence of drug-induced dementia became higher in the chemotherapy group than in the no chemotherapy group and the gap between the two groups appeared to widen over time (Fig. 1, top). The cumulative incidence of drug-induced dementia at 3 years was 12.3 cases per 1,000 persons for the chemotherapy group and 9.7 cases per 1,000 persons for no chemotherapy group, while the cumulative incidence was 16.2 and 13.0 per 1,000 persons at 5 years and 29.0 and 22.8 per 1,000 persons at 10 years for both groups. Similar curves were observed among the matched cohorts (Fig. 1, bottom). However, the patterns of cumulative incidence were different for four other types of cognitive impairments, in which the incidence was lower in patients receiving chemotherapy than those without chemotherapy except for cognitive disorder in which incidence probability overlapped in years 7-12 in both the entire and matched cohorts (data not shown). Fig. 2 presents the cumulative incidence

Table II. Incidence density of cognitive impairments by chemotherapy status and other factors in the entire cohort of patients with colon cancer.

Patient and tumor characteristics	Incidence density of cognitive impairments (number of cases per 1,000 person-years), by chemotherapy status					
	Drug-induced dementia	Alzheimer's disease	Vascular dementia	Cognitive disorder, NOS ^a	Other dementias or dementia, NOS ^a	Any dementia (any of these 5)
Chemotherapy						
Age (years)						
65-69	3.33	3.24	3.92	0.84	4.76	11.16
70-74	2.87	6.09	7.06	0.71	8.06	16.89
75-79	3.74	10.06	12.58	0.49	13.75	26.89
80-84	5.15	15.02	19.25	1.44	20.67	41.83
85-89	3.91	19.95	29.36	0.43	26.44	59.63
Gender						
Male	3.52	6.49	8.33	0.81	9.7	20.09
Female	3.45	8.17	9.86	0.73	10.45	21.64
Tumor stage						
I	2.70	9.78	11.47	0.56	11.82	22.1
II	2.80	7.32	9.32	1.07	10.13	20.54
III	3.16	7.49	9.37	0.57	10.18	20.56
IV	7.82	3.75	5.89	0.71	6.60	20.5
Unstaged	3.42	11.4	9.12	1.21	14.48	26.81
Comorbidity scores						
0	2.96	6.68	7.49	0.7	8.67	17.74
1	3.83	8.44	11.04	1.04	11.56	23.98
≥2	6.04	9.45	15.43	0.59	15.95	34.55
Total	3.48	7.38	9.14	0.77	10.10	20.91
No chemotherapy						
Age (years)						
65-69	1.81	4.13	6.43	0.71	5.95	12.82
70-74	2.65	8.90	12.74	0.82	12.29	24.37
75-79	2.70	14.98	22.22	1.02	20.49	40.59
80-84	3.63	22.43	35.01	1.57	31.87	63.85
≥85	3.77	25.84	48.15	1.41	43.44	89.29
Gender						
Male	2.76	12.08	18.86	1.09	17.61	35.84
Female	2.86	15.46	24.43	1.05	22.39	44.08
Tumor stage						
I	2.40	11.67	16.91	0.89	16.21	31.17
II	2.88	14.75	23.62	1.01	21.66	42.59
III	3.74	20.45	33.01	1.81	31.11	60.89
IV	8.65	18.72	38.06	0.96	31.58	84.29
Unstaged	2.12	18.13	35.3	1.88	27.28	64.14
Comorbidity scores						
0	2.22	12.30	16.8	0.85	16.28	31.53
1	3.19	16.14	27.03	1.22	22.96	47.51
≥2	4.73	17.74	36.15	1.70	33.30	68.01
Total	2.82	14.03	22.06	1.07	20.36	40.56

^aNOS, not otherwise specified.

curve of any dementia (all above dementias combined) over the 15-year period by chemotherapy status. The results were similar to those from the four types of cognitive impairments other than drug-induced dementia.

Table III presents the time-to-event analysis for the hazard ratio of having various types of cognitive impairments. Patients who received chemotherapy were 24% significantly more likely to develop drug-induced dementia compared to those without chemotherapy after adjusting for patient and tumor characteristics (hazard ratio 1.24, 95% CI 1.05-1.47). On the contrast, the risk of developing Alzheimer's disease, vascular dementia, or other dementias was significantly lower in patients receiving chemotherapy than that in those who did not receive chemotherapy, except for cognitive disorder which was not significantly different between the two groups. As expected, the risk of all types of cognitive impairments increased significantly with age and comorbidity scores. There were no significant differences in the risk of developing drug-induced dementia, Alzheimer's disease and vascular dementia between men and women, but women appeared to have slightly lower risks of cognitive disorders and other non-specified dementias. The risk of all types of cognitive impairments was not significantly associated with the receipt of radiation therapy.

Table IV presents the risks of developing cognitive impairments in patients who were treated with chemotherapy compared to those who were not, stratified by the status of mood disorder. The risk of developing drug-induced dementia seemed to be only significantly elevated in those without mood disorder who received chemotherapy compared to those who did not receive chemotherapy in both the entire cohort (hazard ratio 1.26, 95% CI 1.06-1.50) and the matched cohort (1.29, 1.04-1.59). In those who had a history of mood disorder, there was no longer a significant difference in the risk of developing drug-induced dementia between the chemotherapy and no chemotherapy groups (1.13, 0.58-2.18 for the entire cohort; 1.29, 0.52-3.20 for the matched cohort). On the other hand, the risk of developing Alzheimer's disease, vascular dementia or other unspecified dementias was significantly lower in patients receiving chemotherapy compared to those without chemotherapy while the risk of cognitive disorder was not significantly different between the two groups. Also, there was no evidence of effect modification by status of mood disorder. The findings from any dementia (all above dementias combined) were similar to those from the four types of cognitive impairments other than drug-induced dementia.

Discussion

This study found that patients who received chemotherapy were 24% significantly more likely to develop drug-induced dementia compared to those without chemotherapy after adjusting for patient and tumor characteristics. The significantly increased risk was limited to those without a history of mood disorder. The risk of developing Alzheimer's disease, vascular dementia or other dementias was significantly lower in patients receiving chemotherapy than those who did not receive chemotherapy, except for cognitive disorder that was not significantly different between the two groups, which all were not affected by the history of mood disorder. These findings should have important clinical and public health implications,

including key messages about potential chemotherapy-induced dementia but no evidence about chemotherapy associated with the increased risk of other dementias.

Possible relationships between cognitive impairments and chemotherapy have been examined in clinical or community settings involving patients treated with chemotherapy for breast cancer (24-36) and none was conducted in men or women with colorectal cancer. It is important to note that previous pioneering small-scale clinical trials in the 1990s showed a significant association between chemotherapy use and cognitive impairments (24-31). Those small trials with short follow-up times mostly tested the changes in memory and attention which could be reversed after stopping chemotherapy. Our study followed patients up to 17 years after cancer diagnosis, therefore making it possible to examine long-term cognitive impairments such as dementia at the late clinical stages.

The link between chemotherapy and cognitive impairments and its potential mechanisms have been examined in animal models (55-60). For example, it was suggested that deficits in DNA-repair mechanisms and/or a deregulated immune response, coupled with the effect of chemotherapy on these systems, might have contributed to cognitive decline in rats following chemotherapy (56). In another study (59), cyclophosphamide- and doxorubicin-treated rats showed significantly impaired performance on the novel place recognition task compared with untreated controls, suggesting a significant decline in neurogenesis in chemotherapy-treated animals. However, a study by Fremouw *et al* (57) showed that despite significant toxic effects, chemotherapy-treated mice performed as well as control mice on all tasks, concluding that as are some humans, these mice may be resistant to at least some aspects of chemotherapy-induced cognitive decline. Moreover, the study by Fardell *et al* (58) showed that exercising rats had improved cognition relative to non-exercising rats after fluorouracil and oxaliplatin, suggesting that physical activity may help ameliorate the cognitive impairments induced by chemotherapy.

Our study has a number of strengths. First, the study population covered a large cohort of community-based Medicare beneficiaries, leading to much greater generalization of the study findings to the elderly population aged ≥ 65 across the country. Second, a unique feature of our study was that we included only those patients free of any cognitive impairment at the time of cancer diagnosis, thus leading to clearer cause-effect temporal relationships. Third, because of potential selection bias in which some patients with certain characteristics were given chemotherapy while other patients were not given this therapy according to preferences by patients or providers, or because of potential confounding by indication in which whether or not chemotherapy was given was influenced by other conditions such as cognitive decline, mood disorder or other comorbid conditions, the matched cohort analyses based on the conditional probability of receiving chemotherapy would minimize selection bias and potential confounding. In addition, the analysis was further stratified by the status of mood disorder which demonstrated important differences in the associations between chemotherapy use and cognitive impairments. Finally, a large population-based cohort of patients with colorectal cancer were followed-up from 4 to 17 years, allowing for more time to capture chronic

Table III. Relative risk (hazard ratio) of cognitive impairments in the entire cohort of patients receiving chemotherapy compared to those not, controlling for other factors.

Characteristics	Hazard ratio ^a (95% CI) of having cognitive impairments				
	Drug-induced dementia	Alzheimer's disease	Vascular dementia	Cognitive disorder, NOS	Other dementias or dementia, NOS ^a
Chemotherapy					
No chemotherapy	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Chemotherapy	1.24 (1.05-1.47)	0.67 (0.61-0.74)	0.55 (0.50-0.60)	0.78 (0.57-1.07)	0.66 (0.62-0.70)
Age (years)					
65-69	1.00	1.00	1.00	1.00	1.00
70-74	1.08 (0.88-1.32)	2.10 (1.82-2.43)	1.89 (1.67-2.14)	0.98 (0.68-1.42)	1.73 (1.59-1.88)
75-79	1.18 (0.97-1.45)	3.64 (3.17-4.18)	3.32 (2.95-3.72)	1.05 (0.73-1.52)	2.85 (2.63-3.09)
80-85	1.49 (1.20-1.84)	5.70 (4.96-6.56)	5.11 (4.55-5.74)	1.83 (1.27-2.63)	4.41 (4.07-4.78)
85-89	1.37 (1.04-1.79)	6.92 (5.94-8.06)	6.90 (6.09-7.81)	1.46 (0.92-2.33)	6.02 (5.52-6.57)
Gender					
Male	1.00	1.00	1.00	1.00	1.00
Female	1.02 (0.89-1.18)	1.03 (0.96-1.12)	0.98 (0.92-1.04)	0.76 (0.59-0.98)	0.95 (0.91-0.99)
Comorbidity scores					
0	1.00	1.00	1.00	1.00	1.00
1	1.32 (1.13-1.54)	1.26 (1.16-1.36)	1.51 (1.42-1.62)	1.50 (1.14-1.96)	1.38 (1.32-1.45)
≥2	1.85 (1.55-2.20)	1.40 (1.28-1.54)	2.04 (1.90-2.19)	1.81 (1.31-2.49)	1.92 (1.82-2.03)
Radiotherapy					
No	1.00	1.00	1.00	1.00	1.00
Yes	1.06 (0.88-1.27)	0.95 (0.86-1.05)	0.99 (0.91-1.08)	1.12 (0.80-1.56)	0.96 (0.90-1.02)

^aHazard ratio was adjusted for age, sex, ethnicity, marital status, tumor stage, tumor grade, tumor size, number of positive lymph nodes, tumor type, comorbidity, primary surgery, radiation therapy, socioeconomic status, year of diagnosis and SEER areas. The number of cases originally categorized as amnesic disorder was small, therefore those cases were combined with category 'other dementia/NOS'.

Table IV. Hazard ratio of developing cognitive impairments in entire cohort and matched cohort of patients with colon cancer who received chemotherapy compared to those without receiving chemotherapy, stratified by the status of mood disorder.

Type of cognitive impairments	Hazard ratio (95% CI) ^a of having cognitive impairments in patients receiving chemotherapy compared to those who did not, by status of mood disorder prior to cancer diagnosis	
	Had mood disorder	No mood disorder
Entire cohort	(n=2,908)	(n=69,466)
Drug-induced dementia	1.13 (0.58-2.18)	1.26 (1.06-1.50)
Alzheimer's disease	0.66 (0.44-1.00)	0.68 (0.61-0.75)
Vascular dementia	0.49 (0.35-0.68)	0.56 (0.51-0.61)
Cognitive disorder- NOS	0.91 (0.22-3.74)	0.78 (0.56-1.09)
Other dementias or dementia NOS	0.66 (0.48-0.91)	0.64 (0.59-0.69)
Any dementia (any of above)	0.61 (0.48-0.77)	0.67 (0.63-0.71)
Matched cohort	(n=1,193)	(n=30,649)
Drug-induced dementia	1.29 (0.52-3.20)	1.29 (1.04-1.59)
Alzheimer's disease	0.58 (0.35-0.98)	0.65 (0.58-0.73)
Vascular dementia	0.44 (0.29-0.67)	0.53 (0.48-0.58)
Cognitive disorder, NOS	-	0.77 (0.53-1.13)
Other dementias or dementia NOS	0.60 (0.41-0.90)	0.61 (0.55-0.67)
Any dementia (any of above)	0.51 (0.41-0.74)	0.64 (0.60-0.69)

^aHazard ratio was adjusted for age, sex, ethnicity, marital status, tumor stage, tumor grade, tumor size, number of positive lymph nodes, tumor type, comorbidity, primary surgery, radiation therapy, socioeconomic status, year of diagnosis and SEER areas.

conditions such as dementia that would be otherwise missed in short follow-up studies.

It is important to note several important limitations of this study. First, study outcomes only included more serious and late-stage cognitive impairments (such as Alzheimer's disease), which might not be comparable to early stage of cognitive impairments identified in previous clinical trials (19-21,25,26). The claims data did not allow assessment of the early-stage disease process (such as decline in memory or attention) of cognitive impairments. Due to this limitation, our study population who were free of dementia at the baseline might have included those who already had early stage cognitive impairments, which could have affected the association between chemotherapy and outcomes. Second, even though we adjusted for some measured confounding factors and used the matched cohort analysis based on the probability of receiving chemotherapy, there could have been unmeasured or unknown factors which could have influenced physicians to prescribe chemotherapy or not to do so. In particular, if physicians were aware of some studies on potential link between chemotherapy and cognitive impairments, they might hesitate to prescribe chemotherapy to those with suspected cognitive problems. Hence, the potential for selection bias could not be ruled out in this study. Third, the finding that the risk of drug-induced dementia was significantly increased only in those patients without mood disorder may be vulnerable to surveillance bias because of the link between mood disorder and dementia (61). In other words, patients without a history of mood disorder could be more likely labeled by the treating clinicians or

coders as having 'drug-induced dementia', whereas those with a history of mood disorder might be more likely labeled as having dementias other than drug-induced. Similarly, because of difficulty in confirming if a dementia was induced by chemotherapy, clinical or coding staff might likely code a dementia as drug-induced for patients receiving chemotherapy but code differently for patients without receiving chemotherapy, leading to certain degrees of differential misclassification of study outcomes. One way to see if this was the case is to analyze all dementias combined regardless of drug-induced one. We performed additional analyses and found that the receipt of chemotherapy was associated with the decreased risk of all cognitive impairments combined (Tables II-IV and Fig. 2). Fourth, 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 agent but in practice the treating physician might have modified the chemotherapy doses according to each patient's characteristics. Furthermore, this study did not examine the types of chemotherapy utilized, the number of cycles administered, and their potential effects on the outcomes.

In conclusion, there was a significant association between chemotherapy and the risk of developing drug-induced dementia in patients with colorectal cancer who received chemotherapy but did not have a history of mood disorder. This study with long-term follow-up found that the risks of Alzheimer's disease, vascular dementia, or other non-specified

dementias were even lower in patients with colorectal cancer with chemotherapy use than those without this therapy.

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