Chemotherapy and the Risk of Alzheimer's Disease in Colorectal Cancer Survivors: Evidence From the Medicare System

Igor Akushevich, PhD[1]; Arseniy P. Yashkin, PhD[1], Julia Kravchenko, MD, PhD[2]; and Miklos D. Kertai, MD, PhD[3]

QUESTION ASKED: What is the nature of the relationship between exposure to chemotherapy and the risk of onset of Alzheimer's disease (AD) and other neurocognitive disorders (ND) in elderly colorectal cancer survivors enrolled in the traditional Medicare health insurance system?

SUMMARY ANSWER: After inverse probability weighting, chemotherapy was associated with decreased AD risk and lower risk for the majority of other ND including AD-related dementias, dementia (permanent mental disorder), and dementia (senile). The only adverse association to remain significant was cerebral degeneration (excluding AD). The protective effect for the onset of AD was time dependent.

WHAT WE DID: A proportional hazards model was used before and after the use of inverse probability weighting to account for populational differences between the chemotherapy and nonchemotherapy groups. Weights were normalized to the total sample size.

WHAT WE FOUND: After inverse probability weighting chemotherapy was associated with decreased AD risk (hazard ratio [HR], 0.791; 95% CI, 0.758 to 0.824) as well as lower risk for the majority of other ND including AD-related diseases (HR, 0.823; 95% CI, 0.802 to 0.844), dementia (permanent mental disorder; HR, 0.807; 95% CI, 0.782 to 0.832), and dementia (senile; HR, 0.772; 95% CI, 0.745 to 0.801). The only adverse effect to remain significant was cerebral degeneration (excluding AD; HR, 1.067; 95% CI, 1.033 to 1.102). The effects for AD remained after treatment was stratified by chemotherapy agent type and remained significant for up to 6 years past diagnosis.

BIAS, CONFOUNDING FACTOR(S), DRAWBACKS: We were unable to ascertain the severity of AD and other ND in terms of the associated level of cognitive impairment. Therefore, the impact of chemotherapy on the development of milder forms of cognitive impairment, insufficient for a formal clinical diagnosis, could not be assessed. Indeed, a potentially important effect of chemotherapy and related surgical exposures on development of cognitive impairment cannot be completely ruled out. In addition, Medicare claims have limited information on the dose of chemotherapy used, which could influence the occurrence and severity of cognitive impairment.

REAL-LIFE IMPLICATIONS: The results of this study support the hypothesis that receipt of chemotherapy in colorectal cancer survivors is associated with reduced risk for AD. Although additional validation is required, such findings may be used to reduce the potential treatment-related anxiety among patients with cancer worried about the potential adverse effects of guidance-concordant care.

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ASSOCIATED CONTENT

Appendix

Author affiliations and disclosures are available with the complete article at ascopubs.org/journal/op.

Accepted on January 20, 2021 and published at ascopubs.org/journal/op on February 25, 2021: Full-length article available online at DOI https://doi.org/10.1200/OP.20.00729

CARE DELIVERY

original contributions

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abstract

PURPOSE Evidence on the nature of the relationship between patients receiving chemotherapy as an essential part of guideline-concordant cancer care and the onset of Alzheimer's Disease (AD) and other adverse cognitive outcomes has been mixed. Biological mechanisms were proposed to support both a potentially beneficial and an adverse role. To explore the relationship between chemotherapy and onset of AD and other neurocognitive disorders (ND) in colorectal cancer survivors.

METHODS We conducted a retrospective cohort study of 135,834 individuals older than 65 years diagnosed with colorectal cancer between 1998 and 2007, using SEER-Medicare data. A proportional hazards model was used before and after the use of inverse probability weighting to account for populational differences between the chemotherapy and nonchemotherapy groups. Weights were normalized to the total sample size.

RESULTS After inverse probability weighting, chemotherapy was associated with decreased AD risk (hazard ratio [HR]: 0.791; 95% CI: 0.758 to 0.824) and lower risk for the majority of other ND including AD-related diseases (HR: 0.823; CI: 0.802 to 0.844), dementia (permanent mental disorder) (HR: 0.807; CI: 0.782 to 0.832), and dementia (senile) (HR: 0.772; CI: 0.745 to 0.801). The only adverse effect to remain significant was cerebral degeneration (excluding AD) (HR: 1.067; CI: 1.033 to 1.102). The effects for AD remained after treatment was stratified by chemotherapy agent type and remained significant for up to 6 years past diagnosis.

CONCLUSION Chemotherapy use in colorectal cancer survivors demonstrated an association with reduced risk for AD and other ND.

JCO Oncol Pract 17:e1649-e1659.

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on January 20, 2021 and published at ascopubs.org/journal/op on February 25, 2021: DOI https://doi.org/10.1200/OP.20.00729

INTRODUCTION

As the population of cancer survivors grows, the question of the long-term relationship between chemotherapy and cognitive ability becomes increasingly relevent[1] to the health and well-being of the nation's population of older adults. Neuropsychological studies on late cognitive functioning after cytotoxic treatment showed that survivors of breast, ovarian, and lymphoma cancers experienced a decline in cognitive function.[2-6] The most frequently observed cognitive problems were within the domains of memory, processing speed, and executive functioning.[7] In addition, neuroimaging studies on the effects of chemotherapy on brain structure and function found that cytotoxic treatment was further associated with long-term gray matter reductions, global and focal reduced white matter integrity, and altered brain activation during cognitive tasks.[2]

However, epidemiologic studies of the relationship between neurodegenerative dementia and cancer in patients with breast and prostate cancers did not provide consistent evidence.[8-13] Studies reported chemotherapy to be associated with impaired cognitive function,[8] decreasing Alzheimer's Disease (AD) risk,[9,10] no significant effects on subsequent dementia diagnosis,[11] and reduced risk of dementia limited to specific age groups.[12] Most recently, a study of more than 3.5 million elderly veterans[13] found that for most cancers, treatment, including chemotherapy, was associated with a lower risk of AD but an increased risk of the alternative outcomes such as non-AD dementia, stroke, osteoarthritis, and macular degeneration.

Theoretical mechanisms have been proposed to support both a beneficial and an adverse relationship between chemotherapy and subsequent dementia, but no consensus exists to date.[14] Proposed mechanisms supporting an adverse relationship include direct neurotoxic effects on CNS cells caused by crossing of the blood–brain barrier of chemotherapeutic agents[15] and the effect on the CNS blood vessels including reduced blood vessel density in the hippocampus.[16] Alternative mechanisms supporting a potential beneficial effect were centered on the role of neoadjuvant and adjuvant chemotherapy in modulating the risk for AD[17] through suppressing neuroinflammation[18] and/or preventing neuronal cells from entering into the cell cycle and apoptosis.[19]

In general, there is conflicting evidence about the potential role of chemotherapy in the development of cognitive dysfunction of patients who receive chemotherapy.[20,21] In this study, we further explore the relationship between exposure to chemotherapy and the risk of AD using a population of colorectal cancer survivors enrolled in the traditional Medicare health insurance system. Our focus on colorectal cancer was motivated by it (1) being the third most prevalent cancer after prostate and female breast cancer (for which literature on the effect of chemotherapy on AD exists[8-13]), (2) demonstrating comparable prevalence in males and females, (3) being free of sources of confounding related to the effects of other types of therapies (eg, the use of tamoxifen, commonly used in the treatment of female breast cancer, has been associated with cognitive decline[22]), and (4) demonstrating continually declining mortality rates over the last 3 decades,[23,24] allowing affected individuals to live longer, thereby expanding the pool of individuals reaching ages at which AD is commonly ascertained. Finally, since cancer-related cognitive decline does not need to reach the level of an AD diagnosis to be clinically meaningful and AD often coexists with or is misdiagnosed as other neurodegenerative disorders (ND), we include a wide range of these conditions in our analysis.[25]

METHODS

Data drawn from the SEER program linked to administrative health insurance claims records from the Medicare health insurance system (SEER-Medicare) were used for this study.[26] SEER-Medicare provides data on the date of diagnosis, histology, stage, and grade of up to 10 confirmed cancer cases as well as the therapy recommended and/or provided within 4 months of diagnosis, follow-up vital status, cause of death, and basic demographic and area-based socioeconomic characteristics. The Medicare component provides additional information on the diagnoses made (International Classification of Disease 9th edition, Clinical Modification) and procedures performed (Current Procedural Terminology, 4th edition) on all episodes of care paid for by Medicare Parts A and B on a fee-for-service basis.

The initial sample consisted of 287,967 individuals older than 65 years who were diagnosed with colorectal cancer between 1991 and 2007. Individuals without full fee-for-service Medicare Parts A and B coverage 12 months before and 6 months after diagnosis were then excluded, which reduced the sample to 197,564. Then, individuals without at least 6 months of follow-up (−36,272), with a diagnosis of AD and ND at time of diagnosis (−18,807) or with missing data for cancer stage (−6,651), were excluded. After exclusions, the final sample size was 135,834.

The presence of AD and ND, baseline comorbidities, and chemotherapy was identified from Medicare claims using the appropriate diagnosis or procedural codes (Appendix Tables A1 and A2, online only) and algorithms discussed in detail elsewhere.[25,27,28] In addition to a combined measure representing any chemotherapy treatment, eight nonmutually exclusive groups representing the use of individual chemotherapy agents were defined: fluorouracil, irinotecan, oxaliplatin, cetuximab, panitumumab, capecitabine, and other or unspecified chemotherapy.

To evaluate the effect of chemotherapy, individual inverse probability weights (IPWs) were calculated as the reciprocal of the probability to have observed chemotherapy treatment. This resulted in a weighted population pseudorandomized with respect to all predictors used in the treatment model (Appendix Table A2), that is, the only difference between the two groups was the receipt of chemotherapy (and factors not included in the pseudorandomization algorithm). Pseudorandomization is one of the several propensity score–based methods[29] focused on addressing selection bias in observational data. In this approach, individual weights are calculated in such a way as to provide statistical similarity between weighted groups with and without the treatment of interest. No sample loss is involved as the existence of a statistically similar case or control pair is not necessary—the effect is achieved through weighting. Significance testing of pseudorandomization quality (Appendix Table A2) showed that the process was successful. Finally, the effect of the chemotherapy was evaluated using the Cox proportional hazards model with the time-independent indicator of chemotherapy as the only explanatory variable (since all other observable covariates were controlled for in the pseudorandomization process). Individual follow-up was started from the date of colorectal cancer diagnosis. The effect of age was accounted for nonparametrically with age serving as a timescale variable. In this model design, age dependence of AD and ND risks is included in the baseline hazard only. Such models are preferable when age is a strong predictor of the outcome,[30,31] as was the case with AD, for which age is the strongest nongenetic risk factor. Visualizations of group-specific survival functions and log-negative-log survival functions were used to ensure that the proportionality assumption required by the Cox model was satisfied.

RESULTS

Before pseudorandomization, the chemotherapy and nonchemotherapy groups differed significantly across 50 of the 57 variables included in the IPW model (Appendix Table A2). The exceptions were college education, rural residence, non-White race, and the presence of alcohol abuse, diabetes mellitus, septicemia, and HIV at baseline. After pseudorandomization, only one statistically significant difference remained: the presence of other slow-progressing tumor at baseline. The sample pool was 52% female and 93% White; about 50% of the sample was between 70 and 80 years old at baseline, with only 14% older than 85 years. The overwhelming majority of patients were diagnosed with local (45%) or regional (38%) stage cancer, with in situ (6%) and distant (11%) being relatively rare. Only three chemotherapy treatment patterns occurred with sufficient frequency to power further analysis: fluorouracil alone (54%), fluorouracil and irinotecan (9%), and fluorouracil and oxaliplatin (8%). The study-wide incidence rates of AD and ND were AD (7.22%), Alzheimer's disease–related dementias (ADRDs) (18.40%), ADRD with AD excluded (17.40%), dementia/permanent mental disorder (13.02%), dementia/senile (9.35%), vascular dementia (3.28%), cerebral degeneration with AD excluded (11.27%), cognitive deficits or late effects (5.10%), and encephalopathy or not elsewhere classified (4.87%).

Effects of chemotherapy on AD and ND before and after pseudorandomization are presented in Table 1. After pseudorandomization, chemotherapy was associated with decreased AD risk (hazard ratio [HR]: 0.791; 95% CI: 0.758 to 0.824) and lower risk for the majority of other ND including ADRD (HR: 0.823; CI: 0.802 to 0.844), dementia (permanent mental disorder) (HR: 0.807; CI: 0.782 to 0.832), and dementia (senile) (HR: 0.772; CI: 0.745 to 0.801). The only adverse association to remain significant was cerebral degeneration (excluding AD) (HR: 1.067; CI: 1.033 to 1.102). The protective effect for the onset of AD was time dependent (Fig 1): the effect decreased over time, and 7-9 years after colorectal cancer diagnosis, it was no longer significant. When the effect of chemotherapy on AD onset was stratified by the presence of an individual agent (Table 2; Panel A) in the treatment plan or by mutually exclusive agent combinations (Table 2; Panel B), the protective association was consistent across all strata where significant.

DISCUSSION

Our study showed that exposure to chemotherapy was associated with a lower long-term risk for AD. An important finding was that the impacts of chemotherapy varied between specific chemotherapy medications. The association of chemotherapy with reduced risk was also observed, although to a lesser extent, in some other ND. Although before pseudorandomization, receipt of chemotherapy was associated with higher risk for the development of cerebral degeneration and encephalopathy, only the effect associated with cerebral degeneration remained after pseudorandomization.

Our findings show an association between lower risk of AD and ND and chemotherapy receipt in patients with cancer and provide additional independent support to previous findings in this area of study.[9,12,13] Although a recent work already showed that patients with a history of mood disorder who received chemotherapy had significantly lower risk of AD, vascular dementia, and other nonspecified dementia than those without such a therapy,[9] these findings were potentially subject to confounding by unmeasured factors that might have influenced the choice of chemotherapy. In contrast, our analysis included pseudorandomization of patients with cancer, thus mitigating this source of confounding. Furthermore, this study makes a number of novel contributions not found in the literature: we found that lower risk of senile dementia, cognitive deficit as a late effect of cerebral hemorrhage or infarction, and higher risk of cerebral degeneration (excluding AD) was associated with receipt of chemotherapy.

In our study, chemotherapy use was associated with a higher risk for cerebral degeneration, which is a disorder characterized by gradual and progressive loss of neural tissue and neurologic function. There are several potential etiological factors identified for cerebral degeneration including because of alcoholism, cerebrovascular disease, neoplastic disease, Parkinson's disease, and vitamin B12 deficiency. The multifactorial origin and underlying mechanisms of cerebral degeneration in combination with chemotherapy, therefore, highlight the need for future studies with focus on a better characterization of the complex association between exposure to chemotherapy, preexisting conditions, and the risk of cerebral degeneration.

We found an association between chemotherapy and increased risk of encephalopathy (without pseudorandomization) that became nonsignificant after pseudorandomization. Other studies of encephalopathy in patients with cancer were focused on ifosfamide-induced encephalopathy: these studies showed the risk being significantly increased.[32,33] Ifosfamide is an isomer of a cyclophosphamide that is used to treat gynecological, testicular, and head and neck cancers, sarcomas, and lymphomas.[34] Ifosfamide is not used to treat patients with colorectal cancer, and therefore, in our study, no effect was expected. However, another type of encephalopathy discussed in the literature is a posterior reversible encephalopathy syndrome associated with cytotoxic therapies: several studies showed that treatment with irinotecan, leucovorin, and 5-fluorouracil,[35] oxaliplatin and fluoropyrimidine,[36] and capecitabine[37] had neurotoxic effect and increased the risk of encephalopathy. The suggested mechanism for capecitabine was that medication crosses the blood-brain barrier in the form of 5′-DFUR (doxifluridine) and is transformed to 5-fluorouracil in the brain.[37] Our study

TABLE 1. Effects of Chemotherapy on AD and Neurocognitive Disorders

Outcome	HR (95% CI) Before Pseudorandomization	*P*	HR (95% CI) After Pseudorandomization	*P*	No. of Cases (Sample Size)
AD	0.821 (0.784 to 0.860)	< .0001	0.791 (0.758 to 0.824)	< .0001	9,810 (135,834)
ADRDs	0.842 (0.818 to 0.867)	< .0001	0.823 (0.802 to 0.844)	< .0001	24,539 (133,348)
ADRDs, AD excluded	0.833 (0.808 to 0.856)	< .0001	0.819 (0.808 to 0.858)	< .0001	23,268 (133,704)
Dementia (permanent mental disorder)	0.822 (0.794 to 0.852)	< .0001	0.807 (0.782 to 0.832)	< .0001	17,633 (135,389)
Dementia (senile)	0.764 (0.732 to 0.797)	< .0001	0.772 (0.745 to 0.801)	< .0001	12,655 (135,311)
Vascular dementia	0.761 (0.710 to 0.817)	< .0001	0.804 (0.756 to 0.855)	< .0001	4,468 (136,067)
Cerebral degeneration, excluding AD	1.133 (1.095 to 1.173)	< .0001	1.067 (1.033 to 1.102)	< .0001	14,922 (132,456)
Cognitive deficits (late effects)	0.835 (0.791 to 0.881)	< .0001	0.885 (0.843 to 0.929)	< .0001	6,846 (134,157)
Encephalopathy (not elsewhere classified)	1.132 (1.075 to 1.192)	< .0001	1.003 (0.956 to 1.052)	.907	6,609 (135,706)

Abbreviations: AD, Alzheimer's disease; ADRDs, Alzheimer's disease–related dementias; HR, hazard ratio.

suggests that the risk of encephalopathy, at least as related to 5-fluorouracil,[35] irinotecan, leucovorin, and capecitabine,[37] is not present after population heterogeneity is accounted for through pseudorandomization.

The results of our study showed that although capecitabine (antineoplastic antimetabolite agent) and cetuximab (anti-epidermal growth factor [EGF] receptor monoclonal antibody agent) were associated with the lowest risk of AD (0.294), the impacts of irinotecan (cytotoxic quinolone–based alkaloid prodrug, HR: 0.629), oxaliplatin (platinum compound, cytotoxic compound, and inhibitor of DNA replication and transcription, HR: 0.665), and fluorouracil (antineoplastic antimetabolite agent, HR: 0.860) were less pronounced. Some previous studies, predominantly on animal models,[38-40] suggested potential links between AD risk and chemotherapy agent–specific mechanisms. For chemotherapy agents that showed the highest HRs in our study (capecitabine, cetuximab, and panitumumab), no studies focused on associations with AD have been published; however, it has been shown that treatment of older women with stage I-III breast cancer with capecitabine was not associated with a cognitive decline over a 24-month period of observation.[41] In addition, several studies described participation of these agents in pathways that could lead to a lower risk of neurodegeneration. For example, it has been shown that panitumumab and cetuximab as well as several other anticancer EGF receptor inhibitors target a heparin binding EGF-like growth factor gene that has been strongly associated with late-onset AD.[42] This chemotherapy agent has been proposed for retargeting for use in the treatment of injuries of nervous system.

Further detailed analysis of such associations, including the studies of medical records and chemotherapy protocols in patients with different cancers, is needed to investigate the stability of the results obtained in our study. If certain chemotherapy agents have a persistent association with a lower risk of AD, then this information could be useful for further studies on AD treatment. Searching for AD therapies among medications used for cancer treatment is a growing study direction.[43] Structural similarities have been described for AD tau and prostate cancer cell tau, with a correlation between tau levels and cancer response to microtubule-targeting chemotherapy drugs.[44] Neuroprotective effects have been reported for some cancer chemotherapy agents,[45] eg, taxanes have been proposed as potential therapeutic agents for AD,[38] bexarotene was effective in clearing amyloid from the brains of mouse models of AD[39,46] (however, bexarotene was not effective in AD treatment or prevention in recent in vivo studies[47,48]), carmustine reduced beta-amyloid generation and plaque burden in mice,[40] and imatinib reduced amyloid burden and promoted neuroprotection.[49,50] Future investigations are expected to shed light on the spectrum of benefit-to-harm ratio of the effects of chemotherapeutic compounds on CNS along with the alteration of blood-brain barrier and the response of adjacent or other tissues.[14]

Despite the inverse association between chemotherapy and AD observed in our study and others[9,12] and the proposed biological mechanisms, several potential methodological shortcomings should be taken into consideration when interpreting our results. Because of its retrospective nature and reliance on administrative data (which can, for example, misclassify chemotherapy use and contain other data errors), our study outcomes only included late-stage cognitive impairments. However, we believe that the change between the lack of symptoms consistent with a diagnosis and the presence of sufficient symptoms to warrant a diagnosis is a clinically meaningful cognitive change. We were unable to ascertain the severity of AD and the impact of chemotherapy on the development of milder forms of cognitive impairment. Indeed, a potentially important effect of chemotherapy and related surgical exposures on development of cognitive impairment cannot be completely ruled out. Nevertheless, if such an effect exists, based on our findings, it is unlikely that any cognitive impairment related to exposure to chemotherapy results in

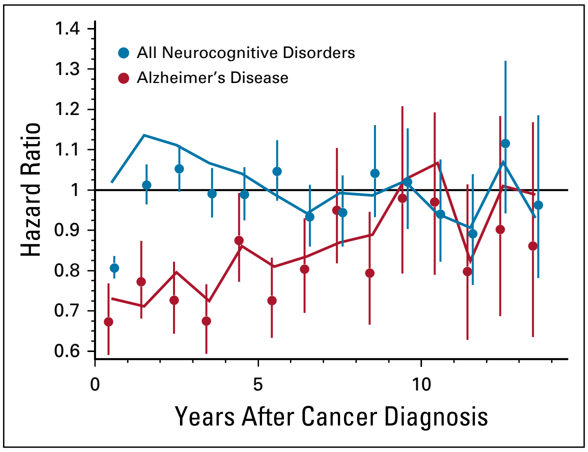

FIG 1. Time-dependent hazard ratios (HRs) associated with exposure to chemotherapy. HRs with 95% CIs after pseudorandomization for Alzheimer's disease (AD) (red dots) and a composite measure of all neurocognitive disorders (ND) (blue dots). HRs with 95% confidence intervals before pseudorandomization for AD (red lines) and a composite measure of all ND (blue lines).

progression to AD. In addition, Medicare claims have limited information on the dose of chemotherapy used, which could influence the occurrence and severity of cognitive impairment. We can envision at least two important scenarios that could lead to the effects observed in our study artificially.

First, our findings can be caused by the competing risk of death. Indeed, in our study, the observed short-term beneficial effect of exposure to chemotherapy can also be explained by premature death, which is assumed to be a censoring event independent of the risk of AD. This dependence can be generated and explained by a simple mechanism: administration of chemotherapy could imply that individuals in poor baseline physical health status are highly likely to die prematurely, and, therefore, these individuals will not have the time to develop AD. In addition, individuals with advanced cancer stages (especially those with metastatic cancer disease) could be less likely to undergo diagnostic testing for AD. We explored these possibilities through a series of sensitivity analyses. Specifically, we estimated the Fine-Gray model, a more realistic model in which deceased individuals continue to contribute to the set of individuals at risk (in the denominator of the partial likelihood) with individual weights dependent on the prevalence of individuals with AD diagnosis in the cohort. The estimate in this case was (HR: 0.725; CI: 0.696 to 0.756) also consistent with our primary findings. Next, we stratified our sample by cancer stage and repeated the analyses (where power allowed). The results were consistent with our primary findings. For example, the associations between receipt of chemotherapy and the risk of AD onset were in situ (HR: 0.642; CI: 0.479 to 0.860), localized (HR: 0.868; CI: 0.803 to 0.939), regional (HR: 0.785; CI: 0.730 to 0.844), and distant (HR: 0.659; CI: 0.522 to 0.834).

Second, individuals with higher cognitive ability could choose chemotherapy more often. However, the frequency of chemotherapy is independent of the quartiles of area-based education measures at the zip code level (39.1%, 38.7%, 38.3%, and 38.5%) and this distribution is further improved after pseudorandomization of chemotherapy groups. We acknowledge the limitation of using area-based measures in lieu of individual-level measures, but the latter were not available in our data.

Finally, in a retrospective study such as ours, there is always a concern that selection of patients for chemotherapy treatment might have been influenced by patient- and disease-specific factors. To control for the potential of such selection bias, we opted for using IPW—a methodology designed to adjust for such inherent differences.

TABLE 2. Effects of Chemotherapy Agents on Alzheimer's Disease

Chemotherapy Agent	HR (95% CI)	*P*
Panel A: any exposure to agent		
Fluorouracil	0.860 (0.815 to 0.908)	< .0001
Oxaliplatin	0.665 (0.551 to 0.803)	< .0001
Irinotecan	0.629 (0.525 to 0.755)	< .0001
Panitumumab	0.455 (0.147 to 1.411)	.1727
Cetuxmimab	0.386 (0.246 to 0.606)	< .0001
Capecitabine	0.294 (0.042 to 2.067)	.2185
Panel B: identified treatment pattern[a]		
Fluorouracil	0.873 (0.825 to 0.924)	< .0001
Fluorouracil plus irinotecan	0.740 (0.590 to 0.927)	.0087
Fluorouracil plus oxaliplatin	0.802 (0.627 to 1.025)	.0775

Abbreviation: HR, hazard ratio.

[a]Only patterns accounting for > 8% of the chemotherapy group are shown.

In conclusion, the results of our study support the hypothesis that receipt of chemotherapy in colorectal cancer survivors is associated with reduced risk for AD after adjusting for patient-, cancer-, and treatment-related characteristics. Furthermore, our findings demonstrated that the association between chemotherapy exposure and AD was not affected by competing risk of long-term mortality. Although additional validation is required, such findings may be used to reduce the potential treatment-related anxiety among patients with cancer worried about the potential adverse effects of guidance-concordant care.

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SUPPORT

Supported by National Institute of Health/National Institute on Aging grants R01-AG-066133 (PI: I.A.), RF1-AG-046860 (PI: A.I. Yashin; Co-PI: I. Akushevich), and R01-AG-057801 (PIs: J.K. and I.A.).

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Collection and assembly of data: Igor Akushevich, Arseniy P. Yashkin
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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/OP.20.00729.

ACKNOWLEDGMENT

The authors are grateful to Anatoliy Yashin for interesting discussions of the methodological and substantive aspects of our analysis and comments.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Chemotherapy and the Risk of Alzheimer's Disease in Colorectal Cancer Survivors: Evidence From the Medicare System

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

APPENDIX

TABLE A1. Administrative Codes Used

	ICD-9/CPT-4/HCPCS Codes
Panel A: study outcomes	
AD	ICD-9 codes for all disorders excluding ADRD and delirium are shown in Table 1 of the reference in footnote 1; ADRD is defined according to the definition shown in Table 1 of the reference in footnote 2; The ICD-9 codes used to identify delirium were 290.11, 290.3x, 290.41, 292.81, 293.0x, 293.1x, 293.81, 293.89, 300.11, 308.xx, 437.xx, 584.xx-586.xx, 780.09.
ADRDs	
ADRDs, AD excluded	
Dementia (PMD)	
Dementia (senile)	
Vascular dementia	
Cerebral degeneration, excluding Alzheimer's disease	
Cognitive deficits (late effects)	
Encephalopathy (not elsewhere classified)	
Panel B: chemotherapy agents	
Fluorouracil	J9190
Irinotecan	J9206
Oxaliplatin	J9263
Cetuximab	J9055
Panitumumab	J9303
Capecitabine	J8520 and J8521
Other or unspecified chemotherapy	
No specific drug name given	V58.1x V66.2x V67.2x
Administration or delivery of chemotherapy; no specific drug name given	G0355-G0363
Chemotherapy-related fatigue	G9021-G9032
Route of administration of chemotherapy	Q0083-Q0085
Management of bladder cancer with BCG	51720
Chemotherapy administration	96400-96549
Other chemotherapy agents (footnote 3)	J9000-J9999
Panel C: comorbidities	
The full list of 49 comorbidities used in this study is listed in Appendix Table A2, together with summary statistics. The associated codes have been previously published in the references in footnote 4 and are not presented here to conserve space.	

NOTE. 1. Akushevich I, Yashkin AP, Kravchenko J, Ukraintseva S, Stallard E, Yashin AI: Time trends in the prevalence of neurocognitive disorders and cognitive impairment in the United States: The effects of disease severity and improved ascertainment. *Journal of Alzheimer's Disease* 64:137-148, 2018. 2. Matthews KA, Xu W, Gaglioti AH, et al: Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥ 65 years. *Alzheimer's & Dementia* 15:17-24, 2019. 3. Excluding codes previously listed. 4. Akushevich I, Yashkin AP, Kravchenko J, Ukraintseva S, Stallard E, Yashin AI: Time trends in the prevalence of neurocognitive disorders and cognitive impairment in the United States: The effects of disease severity and improved ascertainment. *Journal of Alzheimer's Disease* 64:137-148, 2018. Akushevich I, Kravchenko J, Arbeev KG, Ukraintseva SV, Land KC, Yashin AI: Health effects and Medicare trajectories: Population-based analysis of morbidity and mortality patterns. *Biodemography of Aging*:47-93, 2016. Akushevich I, Kravchenko J, Ukraintseva S, Arbeev K, Yashin AI: Age patterns of incidence of geriatric disease in the US elderly population: Medicare-based analysis. *Journal of the American Geriatrics Society* 60:323-327, 2012.

Abbreviations: AD, Alzheimer's disease; ADRDs, Alzheimer's disease–related dementias; BCG, Bacillus Calmette Guerin; CPT-4, Current Procedural Terminology, 4th edition; HCPCS, Healthcare Common Procedure Coding System; ICD-9, International Classification of Disease, 9th edition; PMD, permanent mental disorder.

TABLE A2. Pseudorandomization Quality and Summary Statistics

	Before Pseudorandomization					After Pseudorandomization		
	n Within Group		Percent Within Group			Percent Within Group		
	No Chemo	Chemo	No Chemo	Chemo	Difference in Means (*P*)	No Chemo	Chemo	Difference in Means (*P*)
Year at diagnosis								
2000-2003	25,649	17,730	30.78	33.77	< .0001	31.79	31.85	.9679
2004-2007	24,116	14,741	28.94	28.07		28.59	28.46	
1991-1995	19,875	11,057	23.85	21.06		22.96	22.91	
1996-1999	13,687	8,979	16.43	17.10		16.66	16.78	
Age at diagnosis								
65-69	11,800	12,137	14.16	23.12	< .0001	17.53	17.58	.9959
70-74	17,626	16,044	21.15	30.56		24.91	24.77	
75-79	19,929	14,007	23.92	26.68		24.98	24.98	
80-84	18,239	7,561	21.89	14.40		18.97	19.04	
85 +	15,733	2,758	18.88	5.25		13.61	13.63	
College education								
1st quartile	20,706	13,245	24.85	25.23	.3599	25.40	25.03	.3289
2nd quartile	20,829	13,140	25.00	25.03		25.11	24.91	
3rd quartile	20,942	13,031	25.13	24.82		24.85	24.83	
4th quartile	20,850	13,091	25.02	24.93		24.64	25.23	
Cancer stage								
In situ	7,603	931	9.12	1.77	< .0001	6.28	6.38	.9646
Local	48,359	12,770	58.04	24.32		45.01	44.92	
Regional	22,916	28,306	27.50	53.91		37.66	37.69	
Distant	4,449	10,500	5.34	20.00		11.06	11.01	
Geography								
Midwest	18,408	11,998	22.09	22.85	< .0001	22.64	22.60	.8082
Northeast	18,037	11,663	21.65	22.21		21.89	22.12	
South	10,772	7,341	12.93	13.98		13.28	13.41	
West	36,110	21,505	43.34	40.96		42.18	41.87	
Rural	14,043	8,660	16.85	16.49	.0835	16.70	16.55	.5934
Race or gender								
Female	44,693	25,981	53.64	49.48	< .0001	52.27	51.78	.2033
Non-White	5,857	3,558	7.03	6.78	.0742	7.00	6.87	.4915
Comorbidity at baseline								
Hypertension	58,811	36,317	70.58	69.17	< .0001	70.20	70.17	.9229
MI	4,633	2,253	5.56	4.29	< .0001	5.23	5.02	.2100
Other IHD	33,460	19,218	40.16	36.60	< .0001	39.08	38.67	.2788
Endo- or pericardium	15,858	8,545	19.03	16.27	< .0001	18.17	18.11	.8441
Cardiomyopathy	21,463	12,081	25.76	23.01	< .0001	24.90	24.71	.5660
ARR	33,105	18,544	39.73	35.32	< .0001	38.56	38.22	.3729
HF	20,900	9,189	25.08	17.50	< .0001	22.38	22.39	.9805
Stroke	14,562	7,166	17.48	13.65	< .0001	15.99	15.93	.8436
Stroke with complications	4,162	1,523	4.99	2.90	< .0001	4.22	4.09	.4082

(continued on following page)

TABLE A2. Pseudorandomization Quality and Summary Statistics (continued)

	Before Pseudorandomization					After Pseudorandomization		
	n Within Group		Percent Within Group			Percent Within Group		
	No Chemo	Chemo	No Chemo	Chemo	Difference in Means (*P*)	No Chemo	Chemo	Difference in Means (*P*)
Atherosclerosis	42,046	27,766	50.46	52.88	< .0001	51.57	51.51	.8798
Peripheral vein	11,070	8,696	13.29	16.56	< .0001	14.57	14.81	.4045
Aneurysm/embolism/thrombosis	13,378	7,283	16.05	13.87	< .0001	15.60	15.58	.9324
Nonsolid caner	1,551	2,069	1.86	3.94	< .0001	2.66	2.73	.5295
Breast cancer	2,625	2,634	3.15	5.02	< .0001	3.95	3.94	.9408
Pancreas cancer	363	434	0.44	0.83	< .0001	0.58	0.64	.2994
Kidney cancer	832	770	1.00	1.47	< .0001	1.27	1.23	.6497
Prostate cancer	5,520	4,250	6.62	8.09	< .0001	7.16	7.29	.5010
Melanoma	505	389	0.61	0.74	0.0028	0.69	0.67	.6880
Lung cancer	1,574	2,078	1.89	3.96	< .0001	2.77	2.78	.9570
Other solid slow progressive	6,645	4,487	7.97	8.55	.0002	8.03	8.48	.0294
Other solid fast progressive	10,981	10,988	13.18	20.93	< .0001	16.27	16.31	.8577
Secondary malignant neoplasm	16,775	30,668	20.13	58.41	< .0001	34.94	34.86	.8076
Other nonspecified cancers	26,316	20,656	31.58	39.34	< .0001	35.05	34.97	.8383
COPD	26,254	15,698	31.51	29.90	< .0001	31.44	31.16	.4593
Pulmonary heart	7,603	4,205	9.12	8.01	< .0001	9.00	8.65	.1302
Pneumonia	13,110	7,006	15.73	13.34	< .0001	15.12	14.99	.6709
Other lung	30,366	20,437	36.44	38.92	< .0001	37.84	37.73	.7787
Parkinson	1,146	379	1.38	0.72	< .0001	1.19	1.01	.0785
Depression	7,134	3,723	8.56	7.09	< .0001	8.13	7.88	.2445
Alcohol abuse	1,714	1,022	2.06	1.95	0.1579	2.14	2.08	.6117
Drug or medicine abuse	670	338	0.80	0.64	0.0008	0.75	0.67	.2942
Tobacco abuse	7,695	6,029	9.23	11.48	< .0001	10.30	10.20	.6351
Diabetes	22,433	14,304	26.92	27.24	0.1954	27.46	27.13	.3417
Electrolytes	25,376	16,866	30.45	32.12	< .0001	31.41	31.21	.5907
Chronic liver disease	8,580	8,314	10.30	15.83	< .0001	12.54	12.71	.5325
IBD	10,688	7,938	12.83	15.12	< .0001	13.92	13.64	.2897
Ulcer	6,930	4,069	8.32	7.75	.0002	8.22	8.21	.9643
Gastric bleeding	36,113	22,076	43.34	42.04	< .0001	43.07	43.02	.8857
Renal disease	15,238	9,292	18.29	17.70	.0059	18.28	18.16	.6886
Septicemia	3,741	2,364	4.49	4.50	.9123	4.66	4.48	.2785
HIV	39	35	0.05	0.07	.1267	0.05	0.05	.8517
Anemia	49,459	33,580	59.36	63.95	< .0001	61.37	61.11	.4955
Upper or lower limb fracture	15,106	8,256	18.13	15.72	< .0001	17.14	17.26	.6853
RA	3,237	1,858	3.88	3.54	.0011	3.74	3.86	.4487
Senility	297	141	0.36	0.27	.0054	0.31	0.42	.4244
Low weight	13,318	8,909	15.98	16.97	< .0001	16.72	16.61	.7078
Obesity	3,706	2,578	4.45	4.91	< .0001	4.75	4.56	.2210

Abbreviations: ARR, arrythmia; COPD, chronic obstructive pulmonary disease; HF, heart failure; IBD, inflammatory bowel disease; IHD, ischemic heart disease; MI, myocardial infarction; RA, rheumatoid arthritis.