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Complementary Medicine, Refusal of Conventional Cancer Therapy, and Survival Among Patients With Curable Cancers

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IMPORTANCE There is limited information on the association among complementary medicine (CM), adherence to conventional cancer treatment (CCT), and overall survival of patients with cancer who receive CM compared with those who do not receive CM.

OBJECTIVES To compare overall survival between patients with cancer receiving CCT with or without CM and to compare adherence to treatment and characteristics of patients receiving CCT with or without CM.

DESIGN, SETTING, AND PARTICIPANTS This retrospective observational study used data from the National Cancer Database on 1 901 815 patients from 1500 Commission on Cancer–accredited centers across the United States who were diagnosed with nonmetastatic breast, prostate, lung, or colorectal cancer between January 1, 2004, and December 31, 2013. Patients were matched on age, clinical group stage, Charlson-Deyo comorbidity score, insurance type, race/ethnicity, year of diagnosis, and cancer type. Statistical analysis was conducted from November 8, 2017, to April 9, 2018.

EXPOSURES Use of CM was defined as "Other-Unproven: Cancer treatments administered by nonmedical personnel" in addition to at least 1 CCT modality, defined as surgery, radiotherapy, chemotherapy, and/or hormone therapy.

MAIN OUTCOMES AND MEASURES Overall survival, adherence to treatment, and patient characteristics.

RESULTS The entire cohort comprised 1 901 815 patients with cancer (258 patients in the CM group and 1 901 557 patients in the control group). In the main analyses following matching, 258 patients (199 women and 59 men; mean age, 56 years [interquartile range, 48-64 years]) were in the CM group, and 1032 patients (798 women and 234 men; mean age, 56 years [interquartile range, 48-64 years]) were in the control group. Patients who chose CM did not have a longer delay to initiation of CCT but had higher refusal rates of surgery (7.0% [18 of 258] vs 0.1% [1 of 1031]; $P < .001$), chemotherapy (34.1% [88 of 258] vs 3.2% [33 of 1032]; $P < .001$), radiotherapy (53.0% [106 of 200] vs 2.3% [16 of 711]; $P < .001$), and hormone therapy (33.7% [87 of 258] vs 2.8% [29 of 1032]; $P < .001$). Use of CM was associated with poorer 5-year overall survival compared with no CM (82.2% [95% CI, 76.0%-87.0%] vs 86.6% [95% CI, 84.0%-88.9%]; $P = .001$) and was independently associated with greater risk of death (hazard ratio, 2.08; 95% CI, 1.50-2.90) in a multivariate model that did not include treatment delay or refusal. However, there was no significant association between CM and survival once treatment delay or refusal was included in the model (hazard ratio, 1.39; 95% CI, 0.83-2.33).

CONCLUSIONS AND RELEVANCE In this study, patients who received CM were more likely to refuse additional CCT, and had a higher risk of death. The results suggest that mortality risk associated with CM was mediated by the refusal of CCT.

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Supplemental content

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The use of complementary and alternative medicine (CAM) is estimated to be a multibillion-dollar industry in the United States.[1] Its growth has been attributed to its increased availability and marketing as well as congruence with patients' beliefs, values, and philosophies regarding their health, especially the desire for direct self-autonomy.[1-3] Complementary medicine (CM) is used in addition to conventional cancer therapy (CCT) and may be used as a substitute for adjuvant therapies. There is a broad spectrum of CM used by patients with cancer including herbs and botanicals, vitamins and minerals, traditional Chinese medicine, homeopathy, and naturopathy, as well as specialized diets.[4] Patients with cancer choose to use CM to improve their quality of life and feel more hopeful.[5] Past research has shown that CM therapies such as massage, acupuncture, yoga, and meditation can improve quality of life.[6] Thus, it is estimated that between 48% and 88% of patients with cancer have reported the use of CAM as part of their therapy.[5,7-10]

Despite the widespread use of CAM, there is limited research evaluating the association of CM with survival. We previously investigated alternative medicine (therapy used instead of CCT) and showed that its use (vs nonuse) was associated with an increased risk of death,[11] but we did not investigate CM. Approximately two-thirds of patients with cancer believe that CM will prolong life and one-third expect it to cure their disease.[5] Although it is possible that CM may improve outcomes by helping patients tolerate conventional medical care and complete their recommended therapy, CM may result in inferior survival as a result of delays to receiving proven CCT and refusal of other recommended CCTs.[12-14]

Therefore, in light of the lack of knowledge regarding the association between CM and overall survival in patients with cancer, we used a large national database to identify patients who underwent CM for cancer in addition to CCT. We investigated factors associated with selection of CM, the association between use of CM and delay of initiation of CCT or refusal of further CCT, and how these factors seemed to mediate survival outcomes in patients who used CM compared with those who used no CM.

Key Points

Question What patient characteristics are associated with use of complementary medicine for cancer and what is the association of complementary medicine with treatment adherence and survival?

Findings In this cohort study of 1 901 815 patients, use of complementary medicine varied by several factors and was associated with refusal of conventional cancer treatment, and with a 2-fold greater risk of death compared with patients who had no complementary medicine use.

Meaning Patients who received complementary medicine were more likely to refuse other conventional cancer treatment, and had a higher risk of death than no complementary medicine; however, this survival difference could be mediated by adherence to all recommended conventional cancer therapies.

Methods

Data Source and Construction of the Sample

The National Cancer Database (NCDB) was analyzed for patients who received a diagnosis between January 1, 2004, and December 31, 2013, with 1 of the 4 most prevalent cancers in the United States (breast, prostate, lung, and colorectal cancer).[15] The NCDB is a clinical database that captures approximately 70% of all newly diagnosed cancers from more than 1500 Commission on Cancer-accredited centers in the United States and is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society.

Patients with metastatic disease at diagnosis, stage IV disease based on the American Joint Commission on Cancer in the relevant years of diagnosis (6th edition prior to 2009 and 7th edition after 2009),[16] who received upfront treatment with palliative intent, or with unknown treatment status, clinical, or demographic characteristics were excluded. All patients had to have undergone at least 1 CCT, defined as those who received chemotherapy, radiotherapy, surgery, and/or hormone therapy. Patients were defined as undergoing CM if they received "Other-Unproven: Cancer treatments administered by nonmedical personnel" in addition to any CCT as noted in the patient record. The American College of Surgeons and the Commission on Cancer have not verified and are neither responsible for the analytic or statistical methods used herein, nor for the conclusions drawn from these data by investigators. The Yale Institutional Review Board granted this study exempt status. The informed consent requirement was also waived by the Yale Institutional Review Board because the study was retrospective and the data were deidentified.

Variables

Patient demographic and clinical factors were identified and included cancer type (breast, prostate, lung, and colorectal), American Joint Commission on Cancer clinical stage (I-III), age, race/ethnicity (white, black, Hispanic, or other), sex, Charlson-Deyo comorbidity score (0, 1, or 2), type of primary health insurance (none, private, Medicaid, Medicare, or unknown or government), median income in zip code of residence by quartile (<$48 000 or ≥$48 000), percentage of residents by zip code receiving a high school education (≥80% or <80%), geographic region (Northeast, South Atlantic, Midwest, South, Intermountain West, or Pacific), residence setting (metropolitan or nonmetropolitan), and treatment facility type (academic or community).

Factors Associated With Use of CM

Factors associated with CM were evaluated using the χ^2 test for categorical variables and the *t* test for continuous variables. Independent associations with use of CM were identified using a multivariate mixed-effects logistic regression model that accounted for clustering of treatment patterns based on facility. Since we hypothesized that assignment of CM could vary owing to differences in reporting by facility, random effect owing to clustering by facility was examined.

Matching

Four to 1 nearest-neighbor propensity score matching without replacement (caliper distance of 25% of the SD of the pooled propensity scores) was performed to identify matched cohorts representing the 2 treatment groups.[17] Similar to previously described methods, matching was based on variables identified a priori to be of interest, including age, clinical group stage, Charlson-Deyo comorbidity score, insurance type, race/ethnicity, year of diagnosis, and cancer type.[11] The balance of covariates was evaluated using the standardized difference of means.[18]

Definition of Treatment Delay and Refusal

Treatment refusal was defined as any NCDB-documented refusal of chemotherapy, radiotherapy, surgery, and/or hormonal therapy in the patient record. Treatment refusal did not include patients not receiving treatment because of contraindications or patient risk factors (eg, comorbid conditions or advanced age), nor cases where treatment was recommended but not received for an unknown reason (no reason noted in patient record). Treatment delay was defined as the number of days between diagnosis and first treatment with chemotherapy, radiotherapy, surgery, or hormonal therapy. The association of treatment delay between groups was assessed using 2-sample Wilcoxon rank sum (Mann-Whitney) test and the association of refusal with CM compared with no CM was assessed using the χ^2 test.

Statistical Analysis: Overall Survival

Statistical analysis was conducted from November 8, 2017, to April 9, 2018. Overall survival was defined as the time from diagnosis until death and was the primary outcome of interest. Using the matched sample, univariate survival analyses were completed using the Kaplan-Meier estimator, log-rank test, and Cox proportional hazards regression.

We wanted to assess the association of treatment refusal and treatment delay with survival. To first assess the adjusted association of CM with survival without taking into account treatment refusal (yes vs no) and treatment delay (continuous), a multivariate Cox proportional hazards regression survival model clustered by facility was created. All variables except treatment refusal (yes vs no) and treatment delay (continuous) with $P < .05$ on univariate analyses and Wald $P < .05$ were selected for entry. A preplanned analysis was repeated for each cancer type. Given multiple comparisons, a Bonferroni correction was used for the 4 subgroup analyses, with $P \leq .01$ considered statistically significant.

To then assess the adjusted association of CM with treatment refusal and delay taken into account, a second multivariate Cox proportional hazards regression survival model was created. This model was constructed in the same manner as the above model, except with treatment refusal (yes vs no) and time to treatment from time of diagnosis (continuous variable) included.

The assumption of proportionality for all Cox proportional hazards regression models were verified graphically using log-log survival plots. Statistical analyses were performed using Stata, version 13.1 (StataCorp). All statistical tests were 2-sided and $P < .05$ was considered statistically significant.

Results

Study Cohort Characteristics

Of the 1 901 815 patients in the database, we identified 258 (0.01%) who chose CM. Patient characteristics between those who used CM and those who used no CM are shown in eTable 1 in the Supplement. Patients in the CM group were more likely to be younger than those who used no CM (mean age, 56 vs 62 years; $P < .001$); be female (199 [77.1%] vs 928 242 of 1 901 557 [48.8%]; $P < .001$); have breast cancer (186 [72.1%] vs 732 050 of 1 901 557 [38.5%]; $P < .001$) or colorectal cancer (30 [11.6%] vs 153 605 of 1 901 557 [8.1%]; $P < .001$); be of higher socioeconomic status (≥$48 000 median household income based on zip code of residence; 171 of 253 [67.6%] vs 1 155 676 of 1 882 193 [61.4%]; $P < .001$) and higher educational level (≥80% high school education based on zip code; 179 of 246 [72.8%] vs 1 148 261 of 1 834 001 [62.6%]; $P < .001$); reside in the Intermountain West (26 of 245 [10.6%] vs 80 789 of 1 848 435 [4.4%]; $P < .001$) and Pacific West (94 of 245 [38.4%] vs 228 993 of 1 848 435 [12.4%]; $P < .001$); have private insurance (174 [67.4%] vs 943 203 of 1 901 557 [49.6%]; $P < .001$); have stage I (110 [42.6%] vs 699 627 of 1 901 557 [36.8%]; $P < .001$) and III (54 [20.9%] vs 276 537 of 1 901 557 [14.5%]; $P < .001$) disease; and have a Charlson-Deyo comorbidity score of 0 (237 [91.9%] vs 1 531 339 of 1 901 557 [80.5%]; $P < .001$).

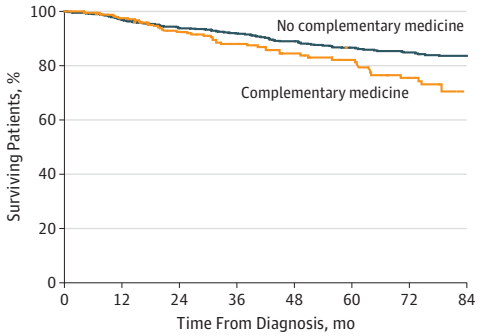
Factors Associated With Treatment Selection

In multivariate logistic regression when controlling for age, cancer type, sex, race/ethnicity, income, educational level, residence setting, geographic area, insurance type, facility type, clinical stage and comorbidity score, patients with breast cancer (odds ratio [OR], 7.26; 95% CI, 3.29-16.02), and colorectal cancer (OR, 4.20; 95% CI, 2.23-7.95) were significantly more likely than those with prostate cancer to receive CM (eTable 2 in the Supplement). Patients who reside in the Intermountain West (OR, 4.65; 95% CI, 2.03-10.64) and Pacific West (OR, 6.61; 95% CI, 3.54-12.37) were independently associated with a greater likelihood of CM selection compared with those who live in the Northeast. Other covariates independently associated with a greater likelihood of CM use included those with clinical stage III (OR, 1.68; 95% CI, 1.12-2.51) compared with stage I disease and those treated at an academic facility (OR, 1.88; 95% CI, 1.22-2.90) compared with a community facility. Patients with a Charslon-Deyo comorbidity score of 1 (OR, 0.51; 95% CI, 0.29-0.90) were less likely to select CM compared with those with a score of 0 (eTable 2 in the Supplement). There was a significant random effect associated with treatment selection at individual facilities (intraclass correlation, 32.6%; 95% CI, 23.6%-43.1%).

Matching

After 4:1 matching, 1032 patients who received CCT were matched to 258 patients who received CM. There were no

Figure. Survival of Patients Who Used Complementary Medicine vs Those Who Used No Complementary Medicine for Breast, Prostate, Lung, and Colorectal Cancer



No. at risk								
No complementary medicine	1022	958	838	691	518	392	294	207
Complementary medicine	256	238	205	167	123	91	72	50

Kaplan-Meier curve for overall survival comparing complementary medicine group with no complementary medicine group.

significant differences in matched characteristics (age, clinical group stage, Charlson-Deyo comorbidity score, insurance type, race/ethnicity, median household income, year of diagnosis, and cancer type). Among other covariates, after matching, patients receiving CM were more likely than the matched cohort to have a higher educational level (high school education ≥80% by zip code; 179 of 248 [72.8%] vs 632 of 991 [63.8%]; $P = .008$) and live in the Intermountain West (26 of 245 [10.6%] vs 47 of 975 [4.8%]; $P < .001$) or Pacific regions (94 of 245 [38.4%] vs 145 of 975 [14.9%]; $P < .001$) (eTable 3 in the Supplement).

Treatment Delay and Refusal

In the matched sample, there was no statistical difference in median delay to CCT from time of diagnosis for patients who used CM compared with those who used no CM (median [interquartile range] time, 29 days [14-50 days] for patients who used CM vs 28 days [15-46 days] for patients who did not; $P = .41$). There was a higher likelihood of refusal of surgery ($\chi^2_3 = 67.32$; n = 1290; $P < .001$; 7.0% [18 of 258] vs 0.1% [1 of 1031]), chemotherapy ($\chi^2_3 = 232.01$; n = 1290; $P < .001$; 34.1% [88 of 258] vs 3.2% [33 of 1032]), radiotherapy ($\chi^2_3 = 346.62$; n = 911; $P < .001$; 53.0% [106 of 200] vs 2.3% [16 of 711]), and hormone therapy ($\chi^2_3 = 240.98$; n = 1290; $P < .001$; 33.7% [87 of 258] vs 2.8% [29 of 1032]).

Survival Outcomes Not Including Treatment Refusal or Delay

On univariate survival analysis, CM was associated with poorer 5-year survival (82.2% [95% CI, 76.0%-87.0%] vs 86.6% [95% CI, 84.0%-88.9%]; log-rank $P = .001$ [**Figure**]; hazard ratio [HR], 1.70; 95% CI, 1.24-2.34 [**Table**]) compared with no CM. Complementary medicine remained an independent associated with a greater risk of death when compared with no CM (HR, 2.08; 95% CI, 1.50-2.90) when controlling for cancer type, age, sex, income, educational level, clinical stage, and Charlson-Deyo comorbidity score (Table). The results did not change significantly when clustering by reporting facility in the regression analysis.

When stratified by cancer type, receipt of CM was associated with statistically significantly poorer 5-year survival for breast cancer (84.8% vs 90.4%; log-rank $P = .001$) and borderline significantly poorer survival for colorectal cancer (81.8% vs 84.4%; log-rank $P = .02$). There were no statistically significant differences seen in 5-year survival for patients with prostate or lung cancer. In multivariate analysis that did not include treatment refusal or delay, receipt of CM was independently associated with greater risk of death for breast cancer (HR, 1.94; 95% CI, 1.24-3.05) and colorectal cancer (HR, 2.61; 95% CI, 1.21-5.60).

Survival Outcomes Including Treatment Refusal or Delay

After also adjusting for treatment refusal (categorical; yes vs no) and delay from diagnosis to treatment (continuous; days), CM (vs no CM) no longer had a statistically significant association with the risk of death (HR, 1.39; 95% CI, 0.83-2.33).

Discussion

Among patients who were receiving at least 1 form of CCT, those who chose CM were more likely to refuse additional CCT. Patients who chose CM also had a higher risk of death than patients who did not use CM when measures of treatment adherence were not included. However, when measures of treatment adherence were included, CM was no longer associated with an increased risk of death. The greater risk of death associated with CM is therefore linked to its association with treatment refusal.

Our evaluation of factors associated with CM use is consistent with the prior literature. We found that CM use (vs nonuse) was associated with variables generally associated with improved survival including younger age, female sex, private insurance, and higher socioeconomic status and educational level. This finding is consistent with prior literature evaluating patient-reported CAM use among patients with cancer, which also demonstrated that patients with cancer and survivors using CAM were more likely to be younger, women, more educated, and have a higher income.[5,10] In addition, we found that patients who used CM were more likely to reside in the Pacific or Intermountain West regions of the United States. This finding, again, is consistent with prior literature that noted "the high concentration of CAM schools in these States, State legislation favoring CAM, and the high concentration of immigrants in these states who may be using CAM."[19(p68)]

We also found an association between a higher stage of cancer and greater likelihood to select CM (vs a lower stage of cancer), which has been unexplored in prior literature, to our knowledge. It is unclear if the higher stage of cancer motivates patients to select CM or if patients who select CM present with more advanced disease as a result of delay in screening or diagnosis, given that the majority of CAM use is intended to prevent illness or disease.[1] There is evidence to suggest that a less hopeful cancer prognosis is associated with use of CM.[20]

Table. Cox Proportional Hazards Regression of Covariates Associated With Overall Survival

	Univariate		Multivariate Model 1	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Treatment type				
No complementary medicine	1 [Reference]		1 [Reference]	
Complementary medicine	1.70 (1.24-2.34)	.001	2.08 (1.50-2.90)	<.001
Age, continuous	1.04 (1.03-1.05)	<.001	1.03 (1.01-1.05)	<.001
Cancer type				
Prostate	1 [Reference]		1 [Reference]	
Breast	3.91 (1.59-9.63)	.003	8.11 (2.86-22.96)	<.001
Lung	53.95 (21.47-135.58)	<.001	53.71 (19.54-147.66)	<.001
Colorectal	7.35 (2.85-18.94)	<.001	5.90 (2.21-15.79)	<.001
Sex				
Male	1 [Reference]		1 [Reference]	
Female	0.69 (0.50-0.93)	.02	0.90 (0.56-1.44)	.66
Race/ethnicity				
White	1 [Reference]		Not included in model	
Black	1.05 (0.62-1.79)	.86		
Hispanic	1.46 (0.37-2.21)	.83		
Other	0.77 (0.43-1.48)	.48		
Income[a]				
<$48 000	1 [Reference]		1 [Reference]	
≥$48 000	0.60 (0.45-0.81)	.001	0.90 (0.63-1.27)	.54
Educational level[b]				
<80% High school education	1 [Reference]		1 [Reference]	
≥80% High school education	0.65 (0.49-0.88)	.005	1.01 (0.71-1.43)	.95
Residence setting				
Metropolitan	1 [Reference]		Not included in model	
Nonmetropolitan	1.20 (0.80-1.78)	.38		
Geographic area				
Northeast	1 [Reference]		Not included in model	
South Atlantic	1.62 (0.96-2.75)	.07		
Midwest	1.22 (0.73-2.04)	.44		
South	1.91 (1.09-3.35)	.02		
Intermountain West	1.50 (0.75-3.02)	.25		
Pacific	1.79 (1.08-2.96)	.02		
Insurance type				
None	1 [Reference]		Not included in model	
Private	0.52 (0.19-1.40)	.20		
Medicaid	1.29 (0.44-3.75)	.64		
Medicare	1.08 (0.39-2.97)	.88		
Government or unknown	0.56 (0.06-5.05)	.61		
Facility type				
Academic	1 [Reference]		Not included in model	
Community	1.20 (0.86-1.66)	.28		
Clinical stage				
I	1 [Reference]		1 [Reference]	
II	1.87 (1.21-2.89)	.005	2.72 (1.72-4.30)	<.001
III	7.99 (5.32-12.0)	<.001	8.01 (5.03-12.77)	<.001
Charlson-Deyo comorbidity score				
0	1 [Reference]		1 [Reference]	
1	3.09 (2.13-4.49)	<.001	0.92 (0.59-1.45)	.74
≥2	1.53 (0.38-6.18)	.55	0.36 (0.08-1.59)	.18

Abbreviation: HR, hazard ratio.

[a] Income is expressed as median household income by zip code of residence.

[b] Educational level is expressed as the percentage of residents by zip code receiving a high school education.

We excluded patients with incurable disease to account for this potential contributor to use of CM.

Our work demonstrates that CM and alternative medicine likely represent entities along a continuum, rather than being distinct entities. Although we consider complementary (or integrative) medicine to integrate unproven nonmedical methods with conventional therapies, and alternative medicine as the use of unproven methods instead of conventional therapies,[21] our work demonstrates that patients who use alternative medicine and CM are often behaving similarly in refusing conventional treatment. As a result, like the patients using alternative medicine[11] (who do not undergo any initial CCT), patients using CM are also placing themselves in an unnecessarily greater risk of death by refusing some CCT.

Limitations

Our analysis is limited by its retrospective and observational nature. The use of CM was likely underascertained given patients' hesitancy to report its use to clinicians and for database registrars to code this use reliably. However, this factor was likely a highly specific variable, which includes only those who actually used 1 or more forms of CM. In addition, it is possible that clinicians were more likely to document the use of CM when patients were using noteworthy therapies that may have resulted in refusal of CCT. There are inherit limitations in retrospective large data collections such as treatment facility selection bias, which may exist because only Commission on Cancer–accredited hospitals contribute data to the NCDB, although the NCDB still captures 70% of newly diagnosed malignant neoplasms and the NCDB has extensive quality assurance mechanisms in place to ensure correct data capture. Consistent with this, we observed that assignment of CM differed significantly by facility. We attempted to account for this variability by clustering by the reporting facility. Other limitations to the data include unmeasured confounders that could influence survival, including lack of data about aversion to cancer screening, refusal of treatment of noncancer-related comorbidities, body mass index, smoking history, burden of disease, functional status, individual income and educational levels, details about incomplete or dose-reduced treatments, and cancer-specific survival. As patients receiving CM were more likely to be female, younger, more affluent, well educated, privately insured, and healthier, we hypothesize that our sample was biased in favor of greater survival for patients who used CM (vs no CM). Information about toxic effects of treatment is not available within the NCDB, and any potential benefits of a treatment modality should be weighed against the possibility of harm and include patient preferences. Last, the absence of information regarding the type and total number of CM modalities used is a limitation. Types of CM previously identified include herbs and botanicals, vitamins and minerals, probiotics, Ayurvedic medicine, traditional Chinese medicine, homeopathy and naturopathy, deep breathing, yoga, Tai Chi, Qi Gong, acupuncture, chiropractic or osteopathic manipulation, meditation, massage, prayer, special diets, progressive relaxation, and/or guided imagery.[4] Therefore, we cannot comment on any specific type of CM and its association with survival. Regardless, except for mind-body therapies that have been shown to improve quality of life,[6] there is limited to no evidence that these therapies have been shown to improve cancer survival as a CM.

Conclusions

We found that, among patients who were receiving at least 1 CCT modality, patients who chose CM were more likely to refuse at least 1 component of CCT and had a higher risk of death than patients who did not use CM. After adjusting for delays and refusal of CCT, CM was not associated with an increased risk of death. We believe our work to be critically important to patients considering CM—a group that likely includes most patients with cancer. Given the hesitance on behalf of patients to disclose nonmedical therapy to their clinicians,[4,5,22] health care professionals need to be proactive in discussing CM and adherence to conventional medicine treatment with their patients. For patients with curable cancers who are inclined to pursue complementary treatment methods, timely adherence to all recommended conventional therapies should be strongly advised.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Johnson, Park, Yu.
Drafting of the manuscript: Johnson, Yu.
Critical revision of the manuscript for important intellectual content: All authors.
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