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Comparing Hospice and Nonhospice Patient Survival Among Patients Who Die Within a Three-Year Window

Stephen R. Connor, PhD, Bruce Pyenson, FSA, MAAA,
Kathryn Fitch, RN, MA, MEd, Carol Spence, RN, MS,
and Kosuke Iwasaki, FIAJ, MAAA

*National Hospice and Palliative Care Organization (S.R.C., C.S.), Alexandria, Virginia;
and Milliman, Inc. (B.P., K.F., K.I.), New York, New York, USA*

Abstract

There is a widespread belief by some health care providers and the wider community that medications used to alleviate symptoms may hasten death in hospice patients. Conversely, there is a clinical impression among hospice providers that hospice might extend some patients' lives. We studied the difference of survival periods of terminally ill patients between those using hospices and not using hospices. We performed retrospective statistical analysis on selected cohorts from large paid claim databases of Medicare beneficiaries for five types of cancer and congestive heart failure (CHF) patients. We analyzed the survival of 4493 patients from a sample of 5% of the entire Medicare beneficiary population for 1998–2002 associated with six narrowly defined indicative markers. For the six patient populations combined, the mean survival was 29 days longer for hospice patients than for nonhospice patients. The mean survival period was also significantly longer for the hospice patients with CHF, lung cancer, pancreatic cancer, and marginally significant for colon cancer ($P = 0.08$). Mean survival was not significantly different (statistically) for hospice vs. nonhospice patients with breast or prostate cancer. Across groups studied, hospice enrollment is not significantly associated with shorter survival, but for certain terminally ill patients, hospice is associated with longer survival times. The claims-based method used death within three years as a surrogate for a clinical judgment to recommend hospice, which means our findings apply to cases where a clinician is very sure the patient will die within three years, and it points to the need to validate these findings. J Pain Symptom Manage 2007;33:238–246. © 2007 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Survival, hospice, palliative care, cancer, congestive heart failure

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Address reprint requests to: Stephen R. Connor, PhD, National Hospice and Palliative Care Organization, 1700 Diagonal Road, Suite 625, Alexandria, VA 22314, USA. E-mail: sconnor@nhpcco.org

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Introduction

The purpose of hospice is to effectively provide palliative care to terminally ill patients and their families, which includes meeting patients' physical, social, spiritual, and emotional needs. The goal of hospice is neither to prolong life nor to hasten the dying process, but

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rather is to maximize patients' quality of life as they travel along this last journey. However, there is a perception among some health care providers that symptom control in palliative care, especially the use of opioids and sedatives, may cause patients to die sooner than they would otherwise. Conversely, preliminary evidence has suggested that the lives of some patients might actually be extended through the use of hospice care.¹⁻⁴

There is a growing body of evidence to counter the argument that the use of opioid and sedative medications for symptom relief hastens death,⁵⁻⁹ even in patients who are receiving high doses of morphine and other opioids.^{5,7} There have been few studies published, however, that have evaluated the effect of hospice care on increasing the longevity of terminally ill patients. In a study on the cost differences between patients who do and who do not elect to receive Medicare-paid hospice benefits,¹⁰ we discovered that costs were lower for patients receiving hospice care and that these costs were not associated with shorter time until death. In fact, in this sample of 8700 patients drawn from the Medicare 5% sample database, the use of hospice appeared to be associated with longer time until death.

Because cost was the focus of our original study, only patients who died during the two-year study period (i.e., 1999 and 2000) were included, which limited the value of the data for a survival study. The fact that patients who chose hospice showed longer mean and median time until death by days to months for all 16 diagnosis categories studied prompted us to investigate our findings further. In the current study, we used a similar methodology to that described in our previous work;¹⁰ however, we limited the cohorts to six that had sufficient numbers for analysis and expanded the study period to include data from 2001 and 2002 in addition to 1999 and 2000 to better measure the survival period.

Methods

In this retrospective cohort study, we used an innovative prospective/retrospective case control method and Medicare administrative data to measure time until death starting from dates that were narrowly defined within

the data. We performed a Kaplan-Meier analysis of the cohorts and used multiple regression models to evaluate the difference of survival periods of terminal illness patients between those using hospices and those not using hospices. For each disease cohort, a set of specific clinical events was used to define an indicative event and a date to measure the beginning point for time to death.

Sources of the Data

From the Centers for Medicare and Medicaid Services, we used Medicare 5% sample data in 1998, 1999, 2000, 2001, and 2002. This data set contains all Medicare-paid claims generated by a statistically representative sample of Medicare beneficiaries. Member identification codes are consistent from year to year and allow for multiyear longitudinal studies. Moreover, this information is generated for both inpatient and outpatient settings. Information includes diagnosis codes, procedure codes, and diagnosis-related group (DRG) codes, along with site of service information, and the amounts paid by Medicare. We used data from 1998 to 1999 to identify cohort members and find the indicative dates of the diagnostics associated with terminal illness. We used the 2000, 2001, and 2002 data to measure the survival periods after the indicative dates.

Additional data were obtained from the Health Care Financing Administration Standard Analytic File of Medicare 5% sample hospice claim data in 1999, 2000, 2001, and 2002, which contain more detailed information on the hospice claims, including hospice start and end dates.

Patient Cohorts

Medicare beneficiaries were identified from 1999 claim data if they met indicative marker criteria for any of the six diseases and died within three years of the indicative marker date. The restriction of the data to people who died within three years of the indicative marker was meant to be a surrogate for clinical judgment, as claim data are not a completely accurate predictor of terminal decline. Strictly speaking, this data restriction means our results apply to cases where a clinician is very sure the patient will die within three years.

The diseases were congestive heart failure (CHF), breast cancer, colon cancer, lung cancer, prostate cancer, and pancreatic cancer. Patients were identified as having one of the six diseases if they had at least one inpatient hospital claim or at least two Part B claims with different service dates with the following ICD-9 codes:

- CHF—428 as the primary diagnosis code;
- breast cancer—174.0–174.9 in any position of the claim;
- colon cancer—153.0–153.9 in any position of the claim;
- lung cancer—162.0–162.9 in any position of the claim;
- prostate cancer—185 in any position of the claim; and
- pancreatic cancer—157.0–157.9 in any position of the claim (except 157.4, islet cell cancer).

Part B claims in the Current Procedural Terminology (CPT) 70,000 or 80,000 series or with Healthcare Common Procedure Coding System (HCPCS) codes beginning with a letter were excluded to avoid potential false positive identification through laboratory or radiology claims. Patients with more than one disease were assigned using the hierarchy: pancreas, colon, lung, breast, prostate, and CHF.

We included only patients who had eligibility in 1998, an indicative date in 1999 and who died within three years after the indicative date. We had no information on whether any of the survivors beyond three years may have chosen hospice after three years. We excluded patients who died within 15 days after the indicative date, as these patients would have had limited opportunity to participate in hospice. We performed a look back to 1998 and excluded patients who had an indicative date in 1998 in an attempt to use the first indicative date for each cohort member.

Patients were divided into hospice and non-hospice cohorts. Patients included in the hospice group were those who had at least one claim for hospice services within three years after the indicative date. The other patients were classified in the nonhospice group.

Indicative Markers

We chose “indicative markers” for the six diagnoses that identified a point in the disease

progression under which a patient could shortly thereafter be advised to consider obtaining hospice care. A thorough description of how these indicative markers were derived for each diagnosis is presented in our earlier paper.¹⁰ In brief, the indicative date for each patient was defined as the date that indicated the beginning of the terminal stage of the disease. Any patient without an indicative date was excluded from the study.

For breast cancer, the indicative date was defined as the maximum date that indicated a switch to another combination of chemotherapy drugs within one to two quarters of the initial chemotherapy. Chemotherapy claims were defined as Part B claims having HCPCS codes of J9000–J9999 (except J9170, Docetaxel). A chemotherapy claim was considered a switching chemotherapy claim if 1) the chemotherapy claim was for a different class of chemotherapy drug from the class of the prior chemotherapy claim *and* 2) the switching chemotherapeutic claim began during the 1–180-day interval after the prior chemotherapy claim.

For colon cancer, the indicative date was defined for three scenarios. First, if there were no colon resection claim, then the indicative date was the minimum date of chemotherapy claims. Second, if a chemotherapy claim occurred within one quarter of the colon resection, then the indicative date was the minimum date of the chemotherapy claims. Third, if the first and second scenario did not apply, then the indicative date was the first date of an intestinal stent claim. Colon resection claims were identified by current procedural terminology (CPT) codes 44140–44160. Chemotherapy claims were identified by CPT codes 96400–96549 and by HCPCS J9000–J9999. Intestinal stent claims were identified by CPT codes 45327, 45345, and 45387.

For lung cancer, the indicative date was defined as the last claim service date of switching chemotherapy or biopsy followed by chemotherapy claims. The definition of switching chemotherapy was the same for lung cancer as for breast cancer, and the definition of chemotherapy claims was also the same as for breast cancer. The definition for a biopsy followed by a chemotherapy claim contained three criteria: 1) the beneficiary had a biopsy claim; 2) a chemotherapy claim followed the

biopsy claim; and 3) the beneficiary had no lung resection claim. The biopsy claim was identified by CPT codes 32405, 10022, and 32400. The lung resection claim was identified by CPT codes 32440, 32480, 32482, 32484, 32486, 32488, 32501, 32520, 32522, and 32525.

For prostate cancer, the indicative date was defined as the minimum date of strontium claims. Strontium claims were identified by a strontium 89 HCPCS code of A9600. For pancreatic cancer, the indicative date was the minimum date of claims having an ICD-9 of 157.0–157.9 (except 157.4, islet cell cancer).

For CHF, the indicative date was defined as the maximum date of a ventilatory management claim when all of the following three criteria were met: there was no coronary artery bypass graft (CABG) claim in the same or next quarter; there was no myocardial infarction (MI) claim in the same quarter; and there was an inpatient claim with a primary diagnosis code of 428 within the same quarter. A ventilatory management claim was identified by intubation and Ventilator Management CPT codes of 94656, 94657, and 31500. CABG claims were identified by CPT codes of 33510 and 33536. A MI claim was defined by the inpatient claim having MI ICD-9 in any position (i.e., acute MI ICD-9: 410.0–410.9).

The hospice and nonhospice cohorts produced by each colon cancer indicative date definition had similar distributions, as did the cohorts using the CHF indicative dates. Thus, there does not appear to be a bias generated by the options within these diseases. We note that it is possible that the final “chemo switching” approach we used for breast and lung cancer may produce shorter survival for nonhospice cohorts if they received more chemo switches after failed therapies.

Statistical Analysis

We analyzed the data using SASTM statistical software (SAS Institute Inc., Cary, NC) and ExcelTM (Microsoft Corporation, Redmond, WA). The dependent variable in our analysis was the length of survival in days. The survival period was defined as the duration between the indicative date and the date of death. The independent variables included the patient’s diagnosis, age, sex, race, and use of hospice. Gehan *P* values for the difference of the two survival curves weighted by the number of survivors

were calculated to analyze the survival periods of hospice and nonhospice patients. This test was performed using SASTM PROC LIFETEST.

A multiple regression model was used to determine the factors that influence survival periods. We limited the model to nine variables to minimize Mallows’ $C(p)$ statistic. The nine variables used in the model were CHF, breast cancer, colon cancer, lung cancer, pancreatic cancer, age category 80–89 years, age category 90+ years, white, and use of hospice. A separate multiple regression model was used to determine the factors that influence survival days for the hospice cohort. This model was also limited to nine variables, which were CHF, breast cancer, colon cancer, lung cancer, pancreatic cancer, age category 60–69 years, age category 70–79 years, Hispanic status, and length of hospice stay.

Results

We identified 4493 patients who met our criteria for the six diseases. Of these patients, 2095 (47%) received hospice care for at least one day. Table 1 summarizes characteristics

Table 1
Description of Study Population (Sample Size)

Variable	Hospice (<i>n</i> = 2095)	Nonhospice (<i>n</i> = 2260)
Disease		
CHF	83 (4%)	457 (20%)
Breast cancer	158 (8%)	136 (6%)
Colon cancer	337 (16%)	215 (10%)
Lung cancer	700 (33%)	586 (26%)
Pancreatic cancer	493 (24%)	386 (17%)
Prostate cancer	324 (15%)	480 (21%)
Age (years)		
<60	72 (3%)	111 (5%)
60–64	115 (5%)	109 (5%)
65–69	440 (21%)	451 (20%)
70–74	554 (26%)	514 (23%)
75–79	482 (23%)	482 (21%)
80–84	268 (13%)	337 (15%)
85–89	119 (6%)	185 (8%)
90+	45 (2%)	71 (3%)
Mean age	73.5	73.9
% Female	45	41
Race		
White	1860 (89%)	1897 (84%)
Black	167 (8%)	259 (11%)
Hispanic	24 (1%)	50 (2%)
Asian	14 (1%)	15 (1%)
Other	30 (1%)	39 (2%)

of the patients. The most common diagnosis was lung cancer for both the hospice cohort and nonhospice cohort (33% and 26%, respectively), and the least common diagnosis was breast cancer (8% and 6%, respectively). The number of patients with colon, lung, and pancreatic cancer was generally higher for the hospice cohort than the nonhospice cohort (a difference of 6%–7% between the cohorts for each diagnosis). The number of patients with CHF was considerably higher for the nonhospice cohort than for the hospice cohort (20% vs. 4%). The age groups were similar for both hospice and nonhospice cohorts, with a mean age of 74 years for both cohorts. Females accounted for 45% of the hospice cohort and 41% of the nonhospice cohort. Whites comprised the majority of the sample (89% and 84% in the hospice and nonhospice cohorts). For the hospice cohort, the mean length of stay in hospice was 43 days but varied by cohort.

Survival Periods

For the entire sample of all disease cohorts, the mean number of survival days was eight days longer for hospice patients than for nonhospice patients (337 vs. 329 days, $P=0.00079$). This difference includes the effects of many factors including demographics and sample sizes of the two cohorts. When we normalized these other factors, the difference in days increases to 29 days, as we show later in the regression.

The survival period was significantly longer for the hospice cohort than for the nonhospice cohort for the following diseases: CHF

(402 vs. 321 days, $P=0.0540$), lung cancer (279 vs. 240 days, $P<0.0001$), and pancreatic cancer (210 vs. 189 days, $P=0.0102$). The survival period was longer for the hospice cohort than nonhospice cohort for colon cancer, and the difference approached but did not reach statistical significance (414 vs. 381 days, $P=0.0792$). Survival plots for CHF, lung cancer, pancreatic cancer, and colon cancer are presented in Figs. 1–4. There was no statistically significant difference between the hospice and nonhospice cohorts for breast cancer (422 vs. 410 days, $P=0.6136$) or prostate cancer (514 vs. 510 days, $P=0.8266$).

Regression Models

The second regression was performed only for hospice cohorts to determine the factors that influence survival days, which are presented in Table 2. The R square was 14.6%. The coefficient of hospice was 29 days, indicating that hospice patients lived longer than patients not using hospice by 29 days. The results of the regression for the hospice cohort are also presented in Table 3.

In the model, the coefficient of length of hospice stay was 0.8. It is not self-evident that the longer hospice days result in the longer survival days, because we define the survival days at the indicative date. However, the results of the regression show that there is a positive correlation between length of hospice stay and the survival days. This result combined with the coefficient of 29 days for the overall regression suggests that a hospice patient lived longer by 0.8 times the number of days in

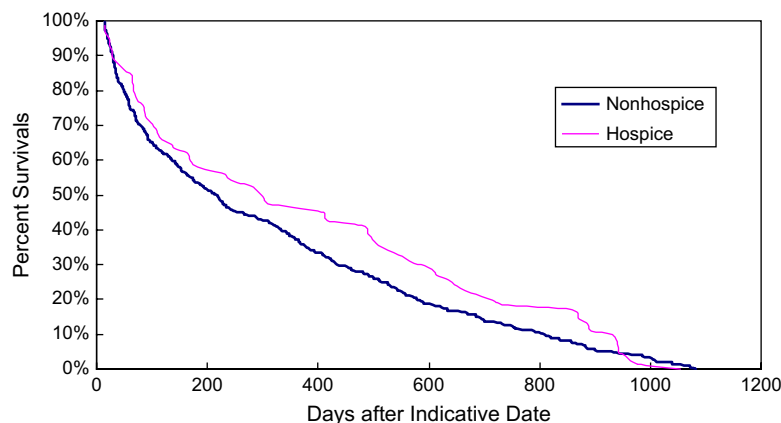


Fig. 1. Survival curve for patients with CHF.

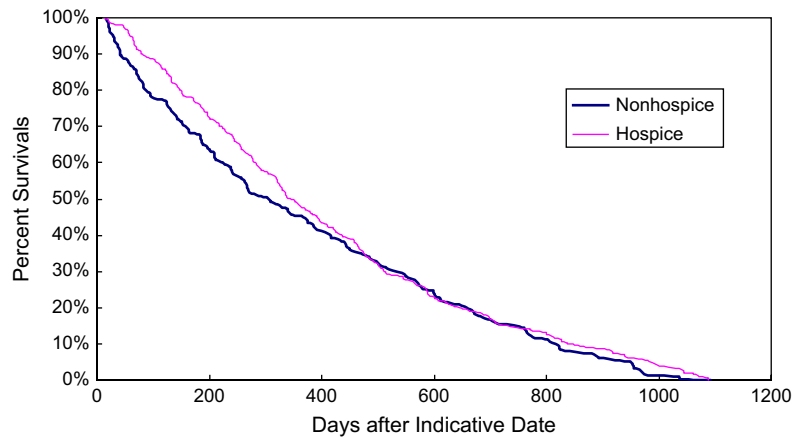


Fig. 2. Survival curve for patients with colon cancer.

hospice. The 0.8 coefficient is close to the overall hospice coefficient (29 days) divided by the average length of hospice days (43 days) ($29/43=0.7$). The positive parameter for the length of hospice stay in the regression model suggests that hospice does not shorten life.

Discussion

Although hospice aims neither to prolong life nor to hasten death, there has been a clinical perception among hospice providers that the use of hospice may actually prolong terminally ill patients' lives, despite the fact that these patients have made the decision to forego further curative treatment. Our

findings suggest that hospice may indeed have a positive impact on patients' longevity or at least not hasten death. We found that for certain well-defined terminally ill populations, patients who choose hospice care live an average of 29 days longer than similar patients who do not choose hospice. This pattern persisted over four of the six disease categories studied, though there was substantial variation in the mean length of survival according to diagnosis. Of note, the largest difference in survival between the hospice and nonhospice cohort was for the CHF patients, where relatively few patients chose hospice care. CHF patients who eventually chose hospice had a mean survival of 402 days compared with 321 days for those who did not.

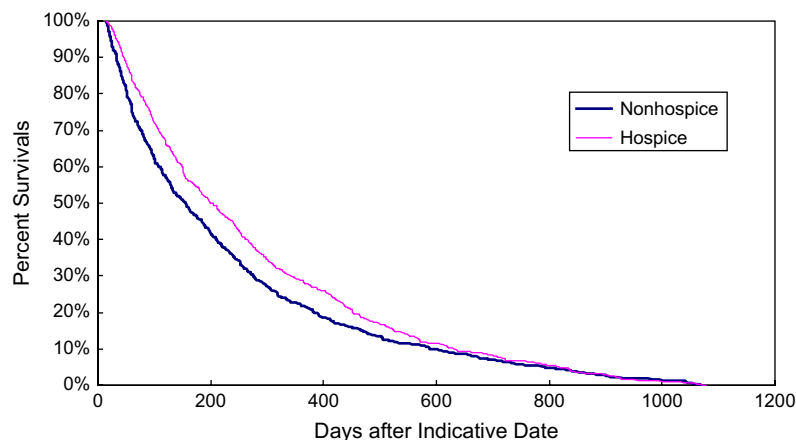


Fig. 3. Survival curve for patients with lung cancer.

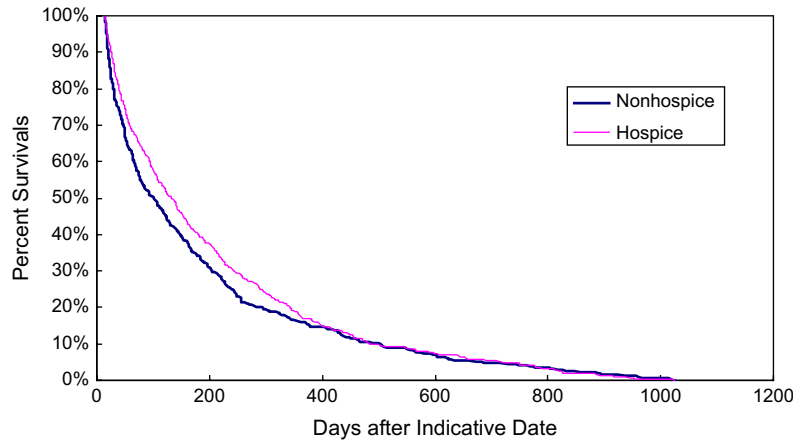


Fig. 4. Survival curve for patients with pancreatic cancer.

Our results are conditional for individuals dying within three years after the indicative event. This means that if a clinician is very sure an individual will die within three years, he or she should think of a recommendation for hospice with longer survival for the selected cohorts. We believe that this is a fairly

strong statement because the three-year survival period we examined is long compared to the average length of hospice stay (43 days in our cohorts).

Our findings are important in helping to dispel the myth that hospice care hastens a patient's death. This myth may stem in part from

Table 2
Results of Overall Regression and Regression of Hospice Cohort

	Overall Regression ^a			Regression of Hospice Cohort ^b		
	Parameters	SE	PValue	Parameters	SE	PValue
Intercept	526	15	<0.0001	454	18	<0.0001
Variables						
CHF	-173	15	<0.0001	-106	32	0.0008
Breast cancer	-104	19	<0.0001	-92	25	0.0002
Colon cancer	-122	15	<0.0001	-104	20	<0.0001
Lung cancer	-261	13	<0.0001	-241	18	<0.0001
Pancreatic cancer	-316	13	<0.0001	-305	18	<0.0001
Prostate cancer	^c	—	—	^c	—	—
Age (years)						
<60	^c	—	—	^c	—	—
60–69	^d	—	—	54	16	0.0009
70–79	^d	—	—	32	14	0.0239
80–89	-17	10	0.1057	^d	—	—
90+	-72	26	0.0054	^d	—	—
Female	^c	—	—	^c	—	—
Male	^d	—	—	^d	—	—
White	-20	—	—	^d	—	—
Black	^d	—	—	^d	—	—
Hispanic	^d	—	—	-102	53	0.0539
Asian	^d	—	—	^d	—	—
Other race	^c	—	—	^c	—	—
Hospice	29	9	0.0008	—	—	—
Length of hospice stay	—	—	—	0.8	0.1	<0.0001

SE = standard error.

^aC(p) value of 8.7985, R-square value of 0.1457; all variables are logical (0 or 1).

^bC(p) value of 8.0347, R-square value of 0.1828; all variables other than length of hospice stay are logical (0 or 1).

^cEliminated for redundancies of variables.

^dEliminated to minimize C(p).

Table 3
Lengths of Hospice Stay for Cohorts

	Number of Hospice Patients = "Count"	ALOHS = μ	Standard Deviation
CHF	83	49	100
Breast cancer	158	40	57
Colon cancer	337	43	62
Lung cancer	700	38	63
Pancreatic cancer	493	47	70
Prostate cancer	324	46	70
All above	2095	43	67

ALOHS = Average length of hospital stay.

the fact that hospice professionals not uncommonly admit patients who are in very poor shape and near death. Indeed, many patients continue to be referred late for hospice or palliative care. The use of opioids and sedatives to alleviate symptoms has also contributed to this perception, though a growing body of literature has amassed to counter this association.⁵⁻⁹

Clinical observation suggests that numerous factors may contribute to the increased longevity we found in patients electing to receive hospice care. First, patients who are already in a very weakened condition avoid the risks of overtreatment when they make the decision to enter hospice. This factor may be particularly relevant to terminally ill oncology patients who forego aggressive cure-directed therapies. Intensive medical interventions such as high-dose chemotherapy or bone marrow transplantation always carry a significant danger of mortality. Second, entering hospice may improve the monitoring and treatment patients receive. The Medicare hospice benefit allows patients to receive medications that might not be covered in the absence of Part D or other insurance, along with interdisciplinary care coordination that rarely occurs in the traditional Medicare program. Third, several studies have suggested that psychosocial supports may tend to prolong life,¹¹⁻¹³ although not all studies have found an association.^{14,15} Nonetheless, for people who are on the edge of survival, constant attention to their emotional well-being and physical health may increase their desire to continue living. Studies of patients with coronary heart disease^{16,17} and breast cancer¹³ have found that low levels of social support increased the risk of

morbidity or death. Without hospice, patients may feel that they are a burden to their family.

Although our findings were consistent across four of the diagnosis categories we studied, it is not clear whether these findings would be replicated in patients with other disease states. In this study we chose very narrowly defined patient cohorts, and further research should be undertaken to determine whether these findings are applicable to other kinds of patients. Not all patients demonstrated increased survival, and it is probably a subset of patients who may benefit. Future research in this area will elucidate the applicability of these findings to other patients.

The methodology used in this study is subject to limitation in the ability to control for selection bias. We do not precisely know if some factors related to the decision to use hospice may be responsible for the results. However, by selecting patients prior to death with the same clinical circumstances rather than selecting patients who died and performing a look back, we believe we have overcome selection bias, at least in part.

This study provides important information to dispel the myth that hospice hastens death and suggests that hospice is related with the longer length of survival by days or months in certain terminally ill patients. This extra time might be particularly important to patients and their families, as it may allow some people to use the end of life as a time of resolution and closure.

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References

1. Christakis NA, Iwashyna TJ, Zhang JX. Care after the onset of serious illness: a novel claims-based dataset exploiting substantial cross-set linkages to study end-of-life care. *J Palliat Med* 2002;5:515-529.
2. Christakis NA. Predicting patient survival before and after hospice enrollment. *Hosp J* 1998;13:71-87.
3. Connor S. *Hospice: Practice, pitfalls, and promise*. Philadelphia, PA: Taylor and Francis, 1998. 118-119.

4. Forster LE, Lynn J. The use of physiologic measures and demographic variables to predict longevity among inpatient hospice applicants. *Am J Hosp Care* 1989;6:31–34.
5. Bercovitch M, Waller A, Adunsky A. High dose morphine use in the hospice setting: a database survey of patient characteristics and effect on life expectancy. *Cancer* 1999;86:871–877.
6. Thorns A, Sykes N. Opioid use in last week of life and implications for end-of-life decision-making. *Lancet* 2000;356:398–399.
7. Morita T, Tsunoda J, Inoue S, Chihara S. Effects of high dose opioids and sedatives on survival in terminally ill cancer patients. *J Pain Symptom Manage* 2001;21:282–289.
8. Good PD, Ravenscroft PJ, Cavenagh J. Effects of opioids and sedatives on survival in an Australian inpatient palliative care population. *Intern Med J* 2005;35:512–517.
9. Vitetta L, Kenner D, Sali A. Sedation and analgesia-prescribing patterns in terminally ill patients at the end of life. *Am J Hospice Palliat Med* 2005;22:465–473.
10. Pyenson B, Connor S, Fitch K, Kinzbrunner B. Medicare cost in matched hospice and non-hospice cohorts. *J Pain Symptom Manage* 2004;28:200–210.
11. Spiegel D, Bloom JR, Kraemer HC, Gottheil F. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989;2:888–891.
12. Berkman LF, Leo-Summers L, Horwitz RI. Emotional support and survival after myocardial infarction. A prospective, population-based study of the elderly. *Ann Intern Med* 1992;117:1003–1009.
13. Kroenke CH, Kubzansky LD, Schernhammer ES, Holmes MD, Kawachi I. Social networks, social support, and survival after breast cancer diagnosis. *J Clin Oncol* 2006;24:1105–1111.
14. Goodwin PJ, Leszcz M, Ennis M, et al. The effect of group psychosocial support on survival in metastatic breast cancer. *N Engl J Med* 2001;345:1719–1726.
15. Kissane DW, Love A, Hatton A, et al. Effect of cognitive-existential group therapy on survival in early-stage breast cancer. *J Clin Oncol* 2004;22:4255–4260.
16. Brummett BH, Barefoot JC, Siegler IC, et al. Characteristics of socially isolated patients with coronary artery disease who are at elevated risk for mortality. *Psychosom Med* 2001;63:267–272.
17. Burg MM, Barefoot J, Berkman L, et al. Low perceived social support and post-myocardial infarction prognosis in the enhancing recovery in coronary heart disease clinical trial: the effects of treatment. *Psychosom Med* 2005;67:879–888.