
Cancer, Comorbidities, and Health-Related Quality of Life of Older Adults

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This study examined the physical and mental health of 126,685 males and females age 65 or over, with and without cancer that completed a Medicare Health Outcomes Survey (MHOS) between 1998-2002. Cancer information was ascertained through the National Cancer Institute's (NCI's) Surveillance, Epidemiology and End Results (SEER) program and linked to MHOS data. Results indicated that across most cancer types, cancer patients reported significantly more comorbid conditions and poorer physical and mental health compared with patients without cancer. Negative associations were most pronounced in those with two or more comorbidities and in those diagnosed with cancer within the past year.

INTRODUCTION

By 2030, the number of Americans age 65 or over is expected to reach 71 million, double the 34.8 million documented in the year 2000, causing an unprecedented shift in the age structure of the U.S. population (Centers for Disease Control and

Prevention, 2007). An individual reaching age 65 today could expect to live an additional 17.9 years, and older adults are increasingly concerned with the quality of those additional years. Advancing age is associated with an increased risk of cancer. Nearly 60 percent of new cancers and more than 70 percent of cancer deaths occur in individuals age 65 or over (Ries et al., 2007). Older age also is associated with other age-related health problems and chronic illness that can have adverse consequences on independent living, rates of disability, and ultimately the quality of life (Bellizzi and Rowland, 2007; Rao and Demark-Wahnefried, 2006; Yancik, 1997). Previous research in community cancer samples has shown high prevalence rates of comorbid conditions among cancer patients, with 69 to 88 percent reporting at least one comorbid condition (Kouroskian, Murray, and Madigan, 2006; Ogle et al., 2000). There is also evidence that cancer patients report more comorbid medical conditions than do patients without a history of cancer (Bellizzi and Rowland, 2007). However, in national survey data, differences have been shown to be small among individuals age 65 or over with 52 percent of cancer patients versus 44 percent of individuals with no cancer history reporting at least one comorbidity (Hewitt, Rowland, and Yancik, 2003). Despite the expected increase in the numbers of people age 65 or over and the age-related nature of cancer and other chronic diseases, very little is known about whether older cancer patients

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have a greater number of comorbid conditions than do older patients without cancer. As a result, population-based research that explores the extent to which normative age-related comorbid diseases contribute to decrements in health-related quality of life (HRQOL) in older cancer patients is needed.

The potential adverse consequences of medical comorbidities pose a major clinical challenge for the care of older cancer patients, and comorbidity has been shown to be an important prognostic factor for patients with cancer (Piccirillo et al., 2004). A review of the literature suggests that in older cancer patients, comorbid conditions and their treatment may interact with cancer treatment and prognosis (Extermann, 2007) and also have been identified as relevant factors in the effects of treatment and mortality of cancer patients (D'Amico et al., 2008; Fouad et al., 2004). Clinicians must make cancer treatment decisions in the context of their patients' pre-existing health problems. We therefore need a more comprehensive understanding of relationships between comorbidities, cancer, and HRQOL to better address the health needs of older cancer patients.

One important data resource to help understand these relationships is the MHOS, conducted by the National Committee for Quality Assurance on behalf of CMS. The MHOS provides information on the HRQOL of Medicare managed care recipients. Previous research using the MHOS has shown that individuals with cancer reported significantly worse HRQOL on all 8 SF-36® scales, than those without cancer (Baker, Haffer, and Denniston, 2003). Data also have shown that the burden of cancer on both physical and mental health is not as great as that of most of the other measured comorbid conditions (Baker, Haffer, and Denniston, 2003; Ko and Coons, 2005). However, in

these studies, all cancer types were collapsed and it was difficult to determine the relative impact of different types of cancer, or the recency of the cancer diagnosis. This has been an issue for large observational studies trying to disentangle effects of cancer and comorbidities on health status, where detailed information on cancer is limited (Bellizzi et al., in press). Having large, national datasets with clinical information on different cancer types and on rarer cancers can help investigators better understand the physical and mental health of older adults and disentangle effects of cancer and the health problems that may also be associated with aging.

The current study extends previous research and examines physical and mental health of individuals age 65 or over with a cancer history (prostate, breast, colorectal, non-small cell lung, endometrial, bladder, melanoma, non-Hodgkin's lymphoma [NHL], and kidney), compared with individuals with no history of cancer. It uses linked data from the MHOS and NCI's SEER program. Because of the large sample, this data linkage project allows greater exploration of the physical and mental health of older adults. Although individuals with cancer are often referred to as survivors, all participants in this article are referred to throughout as patients, as they are all Medicare recipients and can be identified as patients, regardless of their disease status. In this article, we explore relationships between cancer and physical and mental health after accounting for other medical comorbidities. To better understand these relationships, we first compare the prevalence of comorbid conditions for those with and without cancer, and then evaluate whether the number of comorbid conditions varies by cancer type. Based on the literature, we hypothesize that cancer patients will have more comorbidities than patients without a history of cancer. Finally,

we explore variation in physical and mental health by type and number of comorbid conditions and by time since cancer diagnosis in the four most prevalent cancers: (1) prostate, (2) breast, (3) colorectal, and (4) lung cancer. Individuals who are closer to diagnosis are more likely to be in or recovering from treatment. These individuals are more likely to be managing cancer-related symptoms and acute side effects of treatment, which may potentially result in worse HRQOL. We therefore hypothesize that the recency of cancer diagnosis and reporting a higher number of other medical comorbidities will be associated with worse physical and mental health.

METHODS

A detailed description of the SEER-MHOS data linkage is provided by Ambros and colleagues (2008). In brief, the MHOS was designed to measure and track outcomes of care provided by health maintenance organizations to Medicare beneficiaries. It is administered yearly to a random sample of 1,000 Medicare beneficiaries in the managed care plans. Respondents are invited to complete a baseline survey, with a followup survey administered 2 years later. SEER-MHOS linked data includes participants from four MHOS cohorts, with baseline and 2-year followup surveys occurring in 1998 and 2000; 1999 and 2001; 2000 and 2002; and 2001 and 2003. There was an average response rate of 67 percent for the four baseline surveys and among those who responded to the baseline, 81 percent responded to followup surveys. The percentage of MHOS respondents that were in SEER ranged from: 4.0-5.1 percent (depending on the survey). The MHOS includes items that assess demographics, chronic conditions, symptoms, and physical and mental health.

Clinical information on cancer patients was ascertained using the population-based SEER registry data. The SEER program collects information on all cancer cases occurring in a defined geographic area and conducts active followup of all cancer cases. SEER covers approximately 26 percent of the U.S. population from 2000 forward (Ries et al., 2007). Data from the SEER-MHOS linkage began in 1998 and includes 14 out of the 18 currently participating SEER registries and information from the first four MHOS cohorts, representing more than 300 Medicare managed care plans that annually participate in data collection.

Sample

The current study was comprised of participants from the four SEER-MHOS linked cohorts. A cross-sectional dataset was developed which included one survey per person (either baseline or followup) from individuals age 65 or over, yielding a total of 126,685 participants. For participants who completed more than one survey (either because they completed both a baseline and a followup survey or because they participated in more than one cohort), the first survey was used. Cancer patients ($n=14,897$) were identified through SEER, and the first survey completed after their cancer diagnosis was used. Information was ascertained on nine different cancer types including (1) prostate ($n=4,173$), (2) breast ($n=3,237$), (3) colorectal ($n=1,989$), (4) non-small cell lung ($n=621$), (5) bladder ($n=793$), (6) endometrial ($n=756$), (7) melanoma ($n=746$), (8) NHL ($n=405$), and (9) kidney cancer ($n=286$). Individuals with more than one cancer diagnosis, or who self-reported cancer, but were not identified in SEER were excluded. For patients without cancer ($n=111,788$) only those who resided in one of the SEER regions at the time of the survey were included.

Data

Among the survey items available on the MHOS, the current analysis focused on demographic characteristics, self-reported chronic medical conditions (other than cancer), and a standardized HRQOL measure. Demographic variables included age (measured continuously), sex, Hispanic ethnicity, race (yes/no for each of the following: Caucasian, Black, Asian, American Indian, or Other race/multiracial), education (coded as eighth grade or lower, some high school, high school graduate, some college, 4-year college graduate; and more than 4-year college degree), income (coded as <\$10,000; \$10,000-\$19,999; \$20,000-\$29,999; \$30,000-\$39,999; \$40,000-\$49,999; \$50,000-\$79,999; \$80,000 or more), and current marital status (married yes/no and widowed yes/no). Other relevant survey characteristics included indicators for survey mode (mail versus telephone), and whether the individual completed the survey themselves or through a proxy respondent. In addition to cancer status, relevant independent variables included non-cancer chronic medical conditions. Participants self-reported whether they had been told by a doctor that they had any of 12 chronic medical conditions that were listed on the survey as follows: (1) hypertension/high blood pressure, (2) angina/coronary artery disease, (3) congestive heart failure, (4) myocardial infarction/heart attack, (5) other heart conditions, (6) stroke, (7) lung disease (emphysema/asthma/chronic obstructive pulmonary disease [COPD]), (8) gastrointestinal disorders (Crohn's Disease/inflammatory bowel disease [IBD]), (9) arthritis of the hip or knee, (10) arthritis of the hand or wrist, (11) sciatica, and (12) diabetes. Cancer type and time since cancer diagnosis were determined from SEER registry data.

The HRQOL measure is the SF-36[®] health survey, version 1 (Ware and Sherbourne, 1992), a 36-item short-form instrument that is widely used both nationally and internationally. The SF-36[®] yields eight scales that can be combined into two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The PCS and MCS scores make up the primary dependent variables for this article. For all scales, a higher score represents better functioning and well-being. The PCS and MCS are scored on a *T*-score metric, standardized so that a score of 50 represents the average for the U.S. general population (standard deviation [SD] = 10). In the current study, PCS ranged from 2.24 to 78.24, and MCS ranged from -2.46 to 78.65.

Analyses

Analyses were performed using SAS[®] (version 9.1.3). Demographic and background characteristics were tested using chi-square and *t*-tests, with alpha set at 0.01 because of the large sample sizes. Frequencies of the number of comorbid conditions by cancer type were used to describe the sample, and adjusted mean comorbidity counts were estimated using a zero-inflated Poisson regression model. Ordinary least squares regression models were used to assess associations between cancer and PCS and MCS scores and to estimate least squares means among patients with and without cancer. Background characteristics, cancer status, time since diagnosis, and each comorbid condition were included as covariates in the models. We chose to include each comorbid condition in the models, rather than using a comorbidity index (Charlson et al., 1987) because such indices were designed to predict survival outcomes and include diagnoses associated with mortality and not HRQOL

(such as arthritis). Further, several conditions necessary to calculate such indices were not included in the survey (e.g., liver disease and AIDS) and severity information was also not provided. Our final analyses tested the effects of time since diagnosis and number of comorbidities on PCS and MCS scores of individuals with the four most nationally prevalent cancers (prostate, breast, colorectal, and lung cancer). We used specific, planned comparisons that were performed using Tukey's honestly significant difference (HSD) tests (significant at the 0.05 level). These comparisons tested a reference group (the group that was expected to have the worst HRQOL, namely those with two or more

comorbidities and who had been diagnosed with cancer within the past year) compared with individuals with either zero or one comorbid condition and those diagnosed with cancer either 1-5 years or 5 or more years prior.

RESULTS

Sample characteristics are presented in Table 1. The overall sample of 126,685 individuals included 14,897 cancer patients and 111,788 individuals without cancer. The mean age was 74 and the majority of the participants were White, married, and had a high school education or less. Almost 47 percent of the cancer patients

Table 1
Demographic Characteristics and Medical Conditions, by Cancer Status

Demographic	Cancer (N = 14,897)		No Cancer (N = 111,788)		Chi-Square or t-Statistic
	Number	Percent	Number	Percent	
Age, Mean (SD)	75.33	(6.37)	74	(6.40)	23.93***
Sex (Female)	7,198	48.32	64,534	57.73	473.95***
Hispanic	812	5.45	8,864	7.93	114.47***
Black	740	4.97	5,668	5.07	0.29
Asian	702	4.71	5,341	4.78	0.12
Other (Non-Caucasian)	329	2.21	1,282	1.15	
Education (≤High School)	8,405	56.43	66,353	59.35	8.17***
Income (<\$40,000)	9,128	61.27	69,671	62.32	6.17
Married	9,119	61.21	66,245	59.26	20.83***
Widowed	3,955	26.55	31,382	28.07	15.18***
Survey Mode (Mail)	13,161	88.35	98,441	88.06	1.03
Proxy Respondent	1,778	11.94	13,011	11.64	1.12
Comorbid Conditions					
Hypertension	8,054	54.06	59,098	52.87	7.58*
Angina/CAD	2,242	15.05	15,630	13.98	12.39**
Congestive Heart Failure	1,051	7.06	6,868	6.14	18.63***
Myocardial Infarction	1,571	10.55	10,279	9.20	28.28***
Other Heart Condition	3,292	22.10	22,004	19.68	47.96***
Stroke	1,276	8.57	8,335	7.46	23.08***
Emphysema, Asthma, COPD	1,995	13.39	13,342	11.94	26.22***
Crohn's Disease, IBD	838	5.63	5,092	4.56	33.75***
Arthritis—Hip	5,423	36.40	39,434	35.28	7.31*
Arthritis—Hand	4,739	31.81	35,990	32.19	0.88
Sciatica	3,222	21.63	23,641	21.15	1.82
Diabetes	2,577	17.30	17,642	15.78	22.56***

Refer to footnotes at the end of the table.

Table 1—Continued
Demographic Characteristics and Medical Conditions, by Cancer Status

Demographic	Cancer (N = 14,897)		No Cancer (N = 111,788)		Chi-Square or t-Statistic
	Number	Percent	Number	Percent	
Cancer Type¹					
Prostate	4,173	28.01	—	—	—
Breast	3,237	21.73	—	—	—
Colorectal	1,989	13.35	—	—	—
Lung (Non-Small Cell)	621	4.17	—	—	—
Bladder	793	5.32	—	—	—
Melanoma	746	5.01	—	—	—
Endometrial	756	5.07	—	—	—
Non-Hodgkin's Lymphoma	405	2.72	—	—	—
Kidney	286	1.92	—	—	—
Years Since Cancer Diagnosis					
0-1	2,412	16.19	—	—	—
1-5	5,537	37.17	—	—	—
5+	6,948	46.64	—	—	—

* $p < 0.01$.

** $p < 0.001$.

*** $p < 0.0001$.

¹Cancer types listed in order of prevalence.

NOTES: SD is standard deviation. CAD is coronary artery disease. COPD is chronic obstructive pulmonary Disease. IBD is inflammatory bowel disease.

SOURCE: The dataset links the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry data with Medicare beneficiaries' responses to the Centers for Medicare & Medicaid Services' Medicare Health Outcomes Survey (MHOS). The linked SEER-MHOS dataset includes four MHOS cohorts (baseline and followup year): 1998 and 2000; 1999 and 2001; 2000 and 2002; and 2001 and 2003. Data includes responses from the first survey completed per participant.

were diagnosed more than 5 years previously (mean = 6.07 years, SD = 5.59). Cancer patients in this sample reported a higher prevalence for 10 of the 12 different comorbid conditions than did patients without cancer. The two exceptions were comparable rates of sciatica and arthritis of the hand.

Examination of the number of comorbid conditions by cancer type indicated that more than 85 percent of cancer patients and 84 percent of non-cancer respondents reported at least one comorbid condition, and the majority of patients (both those with and without cancer) in the sample reported more than two comorbid conditions. Similar to the unadjusted findings reported in Table 1, after accounting for demographic and other characteristics, patients without cancer reported fewer comorbid conditions than did cancer patients, with the exception of individuals

diagnosed with melanoma, NHL, and prostate cancer (Table 2). Kidney and lung cancer patients reported the highest mean number of comorbid conditions.

After relevant characteristics (Table 1), the number of comorbid conditions, and the time since cancer diagnosis were adjusted, results indicated that all cancer patients except those with melanoma had significantly worse physical health than patients without cancer (Table 3). Overall, lung cancer and NHL patients reported the worst PCS scores, with mean differences from patients without cancer of 5.2 and 4.4, respectively. Lung, NHL, bladder, breast, and colorectal cancer patients reported lower MCS scores than did patients without cancer. Lung cancer and NHL patients reported the worst mental health, but the magnitude of the difference was not as great as it was for physical health.

Table 2
Comorbid Conditions, by Cancer Type

Type	N	Comorbid Conditions			Mean Count ¹	p*
		0	1	2+		
Total	126,685	15.93	22.92	61.15	2.32	—
No Cancer	111,788	16.2	23.03	60.77	2.26	—
Kidney	286	11.89	18.53	69.59	2.57	0.001
Lung	621	11.59	20.93	67.47	2.49	<0.001
Endometrial	756	9.66	22.88	67.46	2.41	0.005
Bladder	793	13.11	21.06	65.82	2.45	<0.001
Colorectal	1,989	12.62	22.62	64.75	2.37	0.001
Breast	3,237	12.48	22.12	65.41	2.36	<0.001
Prostate	4,173	15.22	22.86	61.93	2.32	0.022
Melanoma	746	15.82	23.46	60.71	2.26	0.944
Non-Hodgkin's Lymphoma	405	15.06	21.48	63.45	2.25	0.931

*p-value comparing the adjusted mean number of comorbidities in non-cancer sample, <0.01 is considered significant.

¹Adjusted for age, sex, education, income, race, ethnicity, marital status, survey type, proxy response; means compared to no cancer.

SOURCE: The dataset links the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry data with Medicare beneficiaries' responses to the Centers for Medicare & Medicaid Services' Medicare Health Outcomes Survey (MHOS). The linked SEER-MHOS dataset includes four MHOS cohorts (baseline and followup year): 1998 and 2000; 1999 and 2001; 2000 and 2002; and 2001 and 2003. Data includes responses from the first survey completed per participant.

Table 3
Health-Related Quality of Life of Cancer Patients Compared to Patients Without Cancer, Accounting for Other Medical Comorbidities

Type	Physical Component Summary Score ¹		Mental Component Summary Score ¹	
	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
No Cancer	42.72	0.03	51.73	0.03
Lung	37.47*	0.41	48.52*	0.45
Non-Hodgkin's Lymphoma	38.30*	0.51	49.78*	0.56
Kidney	39.76*	0.60	50.46	0.66
Endometrial	41.16*	0.37	52.62	0.41
Colorectal	41.32*	0.23	51.00*	0.25
Breast	41.55*	0.18	50.95*	0.20
Prostate	41.58*	0.16	51.09	0.18
Bladder	41.71*	0.36	50.59*	0.40
Melanoma	42.79	0.37	51.7	0.41

* Significantly different by Tukey's honestly significant difference test from "No Cancer" group, p<0.05.

¹ Adjusted for age, sex, education, income, race/ethnicity, marital status, survey type, proxy response, time since cancer diagnosis, and non-cancer comorbidities.

SOURCE: The dataset links the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry data with Medicare beneficiaries' responses to the Centers for Medicare & Medicaid Services' Medicare Health Outcomes Survey (MHOS). The linked SEER-MHOS dataset includes four MHOS cohorts (baseline and followup year): 1998 and 2000; 1999 and 2001; 2000 and 2002; and 2001 and 2003. Data includes responses from the first survey completed per participant.

Table 4 shows the estimated coefficients for each cancer type and each comorbid condition from the PCS and MCS multiple regression models. It provides information on the relative influence of each chronic condition, including cancer types, on both physical and mental health outcomes. Results showed that taken together, non-cancer lung disease (emphysema/asthma/COPD), lung cancer, and sciatica had the greatest negative impact on both PCS and MCS scores. For physical health, arthritis of the hip had the largest negative association, and among cancer diagnoses, NHL had the greatest negative association after lung cancer. Gastrointestinal disorders (Crohn's Disease and IBD) had the greatest negative impact on mental health, followed by stroke and lung cancer.

Table 5 presents results for HRQOL among the most prevalent cancers (prostate, breast, colorectal, and lung) by number of comorbid conditions, and time since cancer diagnosis. Post-hoc planned comparisons were conducted on PCS and MCS scores; the reference group for each cancer type included individuals who had a cancer diagnosis in the last year and had two or more other comorbid conditions. Among prostate cancer patients, compared with the reference group, individuals with fewer comorbid conditions reported better PCS scores regardless of the recency of their diagnosis. Similar results were found for breast, colorectal, and lung cancer patients. Individuals who were diagnosed with their respective cancer in the past year, but had only one comorbid condition were not statistically significantly different from the reference group (those with two or more comorbidities).

Across all four cancers, compared with the reference group, individuals diagnosed with cancer within the past year reported statistically comparable MCS scores, regardless of the number of comorbidities.

Additionally, those with two or more comorbid conditions (regardless of the time since diagnosis) reported similar MCS scores in each cancer group. In breast and colorectal cancer patients, compared with the reference group, MCS scores were significantly higher among individuals who had fewer than two comorbidities if they were diagnosed with cancer more than a year previously. In lung and prostate cancer patients, those diagnosed more than a year previously also had no comorbidities, and those diagnosed 5 years or more previously with one comorbid condition reported better MCS scores than the reference group.

DISCUSSION

This study examined relationships among cancer, comorbidity, and physical and mental health in the SEER-MHOS data linkage project. Results indicated that across most cancer types, after adjusting for demographic differences, individuals with a cancer history have a small, but significantly higher, prevalence of most of the comorbid medical conditions measured on the MHOS. After also accounting for these medical comorbidities and the time since cancer diagnosis, results showed that cancer patients (other than those with melanoma) had significantly worse physical health compared with patients without cancer. Non-small cell lung, NHL, breast, colorectal, and bladder cancer patients also reported worse mental health than did patients without cancer. On further investigation of the four most prevalent cancers in the U.S. (prostate, breast, colorectal, and lung cancer), we saw that negative associations with physical and mental health were most pronounced in those with two or more comorbidities, and in those diagnosed with cancer within the past year. Thus, our main hypotheses were supported. These results highlight

Table 4
Impact of Chronic Conditions on Health-Related Quality of Life, Ordered by Magnitude of Influence

Condition	Beta Estimate	Standard Error	<i>t</i>	<i>p</i>
Physical Component Summary				
Arthritis—Hip	-5.99	0.07	-88.52	<.0001
Emphysema, Asthma, COPD	-5.30	0.09	-59.47	<.0001
Non-Small Cell Lung Cancer	-5.26	0.41	-12.82	<.0001
Non-Hodgkin’s Lymphoma	-4.43	0.51	-8.74	<.0001
Sciatica	-4.13	0.07	-56.12	<.0001
Congestive Heart Failure	-3.95	0.13	-29.92	<.0001
Stroke	-3.93	0.11	-35.08	<.0001
Kidney Cancer	-2.96	0.60	-4.92	<.0001
Diabetes	-2.91	0.08	-36.01	<.0001
Crohn’s Disease, IBD	-2.31	0.14	-16.84	<.0001
Arthritis—Hand	-2.20	0.07	-32.09	<.0001
Angina	-2.02	0.10	-20.61	<.0001
Other Heart Conditions	-1.99	0.08	-26.05	<.0001
Endometrial Cancer	-1.57	0.37	-4.21	<.0001
Hypertension	-1.52	0.06	-25.56	<.0001
Colorectal Cancer	-1.40	0.23	-6.06	<.0001
Breast Cancer	-1.17	0.18	-6.38	<.0001
Prostate Cancer	-1.14	0.16	-6.95	<.0001
Myocardial Infarction	-1.08	0.12	-9.16	<.0001
Bladder Cancer	-1.01	0.36	-2.79	0.0053
Melanoma	0.06	0.37	0.17	0.8646
Mental Component Summary				
Crohn’s Disease, IBD	-3.76	0.15	-24.82	<.0001
Stroke	-3.45	0.12	-27.89	<.0001
Non-Small Cell Lung Cancer	-3.22	0.45	-7.10	<.0001
Emphysema, Asthma, COPD	-2.25	0.10	-22.83	<.0001
Sciatica	-2.17	0.08	-26.69	<.0001
Congestive Heart Failure	-2.02	0.15	-13.83	<.0001
Non-Hodgkin’s Lymphoma	-2.02	0.26	-3.50	0.0005
Diabetes	-1.46	0.09	-16.37	<.0001
Arthritis—Hand	-1.40	0.08	-18.46	<.0001
Kidney Cancer	-1.27	0.67	-1.91	0.0555
Other Heart Conditions	-1.16	0.08	-13.77	<.0001
Angina	-1.15	0.11	-10.55	<.0001
Bladder Cancer	-1.14	0.40	-2.84	0.0045
Breast Cancer	-0.79	0.20	-3.89	<.0001
Colorectal Cancer	-0.74	0.25	-2.89	0.0039
Prostate Cancer	-0.64	0.18	-3.53	0.0004
Arthritis—Hip	-0.53	0.07	-7.05	<.0001
Hypertension	-0.44	0.07	-6.76	<.0001
Myocardial Infarction	-0.08	0.13	-0.63	0.5317
Melanoma	-0.03	0.41	-0.08	0.9331
Endometrial Cancer	0.89	0.41	2.16	0.0308

NOTES: COPD is chronic obstructive pulmonary disease. IBD is inflammatory bowel disease.

SOURCE: The dataset links the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) cancer registry data with Medicare beneficiaries’ responses to the Centers for Medicare & Medicaid Services’ Medicare Health Outcomes Survey (MHOS). The linked SEER-MHOS dataset includes four MHOS cohorts (baseline and followup year): 1998 and 2000; 1999 and 2001; 2000 and 2002; and 2001 and 2003. Data includes responses from the first survey completed per participant.

Table 5

Health-Related Quality of Life, by Number of Comorbid Conditions and Recency of Cancer Diagnosis Among Prostate, Breast, Colorectal, and Non-Small Cell Lung Cancer Patients

Cancer Type and Time Since Diagnosis	n	Physical Component Summary Score by Number of Comorbidities						Mental Component Summary Score by Number of Comorbidities					
		0		1		2+		0		1		2+	
		Mean ¹	Standard Deviation	Mean ¹	Standard Deviation	Mean ¹	Standard Deviation	Mean ¹	Standard Deviation	Mean ¹	Standard Deviation	Mean ¹	Standard Deviation
Prostate	4,173												
0-1 Year	643	47.71*	10.70	45.20*	11.31	37.69	11.42	53.54	9.07	52.46	11.37	50.17	12.55
1-5 Years	1,768	50.36*	9.13	47.55*	9.68	38.91	11.95	54.89*	8.99	53.72	9.89	50.09	12.55
5+ Years	1,762	48.40*	10.19	46.14*	11.27	37.86	11.94	54.11*	10.16	54.15*	9.71	49.85	12.89
Breast	3,237												
0-1 Year	432	46.73*	9.98	42.88	11.60	35.15	11.97	51.89	10.78	50.45	13.39	48.6	13.06
1-5 Years	1,112	48.44*	10.52	46.83*	10.60	36.76	11.98	54.36*	10.61	53.41*	10.14	48.91	13.73
5+ Years	1,693	50.14*	9.27	46.18*	10.89	37.03	12.40	54.46*	9.24	53.32*	9.96	49.46	13.47
Colorectal	1,989												
0-1 Year	330	41.82*	13.36	43.09	11.16	34.83	12.05	50.83	12.37	49.26	12.76	46.84	13.85
1-5 Years	737	47.15*	10.88	45.33*	10.78	37.03	11.92	52.86*	10.89	54.43*	10.79	49.36	13.33
5+ Years	922	47.84*	10.40	46.90*	10.71	37.65	12.71	53.34*	11.00	52.43*	11.39	49.26	13.11
Lung	621												
0-1 Year	191	40.85*	14.20	33.18	10.35	31.03	11.67	49.49	12.10	46.35	14.35	42.82	15.13
1-5 Years	248	42.47*	14.31	38.77*	13.02	33.38	11.16	53.65*	10.57	49.88	12.10	46.56	14.21
5+ Years	182	48.49*	7.53	43.42*	11.91	35.88	12.38	55.03*	5.02	55.23*	6.54	47.53	14.73

* Significantly different by Tukey's honestly significant difference test from reference group (shaded)—individuals with 2 or more comorbidities who were diagnosed with cancer in the past year, $p < 0.05$.

¹ Adjusted for age, sex, education, income, race/ethnicity, marital status, survey type, proxy response.

SOURCE: The dataset links the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry data with Medicare beneficiaries' responses to the Centers for Medicare & Medicaid Services' Medicare Health Outcomes Survey (MHOS). The linked SEER-MHOS dataset includes four MHOS cohorts (baseline and followup year): 1998 and 2000; 1999 and 2001; 2000 and 2002; and 2001 and 2003. Data includes responses from the first survey completed per participant.

the importance of examining associations between cancer and HRQOL by specific cancer types, and accounting for the recency of diagnosis and presence of other medical comorbidities. The SEER-MHOS data linkage provided a unique opportunity to investigate these relationships in a large sample of older adults.

Overall, cancer patients had a high prevalence of at least one comorbid condition (ranging from 84 to 88 percent) as did individuals without cancer (83 percent). These data are generally consistent with previous studies (Koroukian, Murray, and Madigan, 2006; Ogle et al., 2000). When compared with patients without cancer, the magnitude of the differences in our study were modest, with cancer patients in this sample having only 1 to 3 percent higher prevalence estimates for other comorbid conditions. This is not surprising, as many cancers and other chronic health conditions have similar risk factors such as smoking, obesity, physical inactivity, and poor diet. Previous estimates using national data have shown that overall, a higher percentage of cancer patients report at least one comorbid condition compared with patients without cancer (Hewitt, Rowland, and Yancik, 2003). However, prevalence estimates were not as disparate among individuals age 65 or over. In our study, when the number of comorbid conditions was examined by cancer type, it became clear that among patients with certain cancers, particularly melanoma and NHL, the adjusted number of reported comorbid conditions was no higher than for patients without cancer, and that prostate cancer patients had only a marginally higher mean number of comorbid conditions. Conversely, among individuals with kidney, lung, endometrial, bladder, colorectal, and breast cancer, the number of comorbid conditions was significantly higher. The percentage of patients with these cancer diagnoses reporting one

or more comorbid condition was approximately 3 to 6 percent greater than was the case for patients without cancer. These data suggest that it is important to separate out types of cancer when investigating the role of other comorbid medical conditions in HRQOL.

Examination of physical and mental health indicators revealed that across most cancer types, cancer patients had statistically significantly lower scores than did patients without cancer after accounting for other medical comorbidities, the time since cancer diagnosis, and other relevant characteristics such as age. Results from this study also provided some information about the relative impact of chronic diseases, including cancer, on HRQOL. In general, results showed that most non-cancer comorbidities had stronger associations with both PCS and MCS than cancers (i.e., they generally had larger coefficients) and were more efficient predictors, evidenced by the smaller standard errors. Data indicated that arthritis and lung disease had the greatest impact on physical health, whereas gastrointestinal disorders and strokes had the greatest negative impact on mental health. These findings are important, as they indicated that cancer patients may have many competing comorbidities that are relevant to HRQOL, and in some cases have a stronger impact than the cancer itself.

Closer examination of HRQOL in cancer versus non-cancer patients indicated that compared with patients without cancer, lung and NHL patients reported the worst physical and mental health. However, in samples this large, it is also important to examine the magnitude of the differences as well as their statistical significance. Different criteria have been used in the literature to indicate the minimally important difference (MID) necessary to signify a meaningful or clinical effect (Guyatt, Walter,

and Norman, 1987). Cohen's (1992) criteria suggest that a small effect is indicated by a 0.20 SD and a 0.50 SD is a medium effect size. There is support in the literature that MID's fall within this range (Hays, Farivar, and Liu, 2004; Kosinski et al., 2000). In this case, a 2 to 5 point difference, or greater on the PCS and MCS would be considered large enough to be important.

For both lung cancer and NHL, physical health scores were close to one-half of a SD (5 points) lower than were those of patients without cancer. These differences indicate a medium effect, and exceed estimates of MID's for the SF-36® (Ware et al., 1993; Hays and Morales, 2001). So in addition to statistical significance, these results also suggest clinically meaningful differences in some cancers. The importance of identifying this difference is because cancer care often fails to address patients' HRQOL issues in cancer survivors (Institute of Medicine, 2008). These findings suggest that health care providers, particularly those focused on caring for lung and NHL survivors, should provide appropriate support services to attenuate the adverse HRQOL consequences of cancer and its treatment. Additionally, these findings illustrate the need for policymakers and payers to make it possible for clinicians to provide these services by reimbursing them for this service. It is important for health care providers to consider the impact of cancer on HRQOL when caring for patients with these cancers. In addition, it is important for policymakers to begin to support the integration of HRQOL data in clinical care.

We were able to further explore associations between comorbidities and time since cancer diagnosis within the most prevalent cancers (prostate, breast, colorectal, and lung cancer patients). Results indicated that individuals with the greatest number of comorbid conditions, who were

also diagnosed with cancer in the previous year, had the worst HRQOL across both physical and mental health. Those individuals recently diagnosed with cancer are likely to be in treatment or recovering from treatment and its associated acute side effects. It is possible that more attention needs to be paid to controlling these symptoms as they are known to adversely affect HRQOL (Hodgson and Given, 2004; Kurtz et al., 1999). Further, it appeared that having a greater number of comorbid conditions was a stronger indicator of lower PCS and MCS scores than was time since diagnosis. These findings have important implications, particularly for long-term cancer care. While those closer to diagnosis are typically managing side effects of cancer and treatment, and therefore report worse physical and mental health, these results suggest that multiple chronic conditions may have important effects in long-term survivors.

Although results showed fairly consistent patterns across cancer types, differences were most pronounced among lung cancer patients, where the difference in scores for those with the most comorbid conditions, diagnosed in the past year, to those with no comorbid conditions diagnosed more than 5 years ago, was 17 points on the PCS and 12 points on the MCS. However, lung cancer patients who survive for 5 years or who have no comorbid conditions are likely to be very different from most lung cancer patients. Lung cancer patients age 65 or over have a 5-year survival rate of 14 percent (Surveillance, Epidemiology, and End Results Program, 2007) and the prevalence of comorbid conditions associated with smoking such as cardiovascular disease and COPD have been shown to be higher than the general population (Janssen-Heijnen et al., 1998). While it appears that long-term survival is associated with better HRQOL in lung cancer patients, this is likely due to

a healthy survival effect, as individuals with greater disease severity were not as likely to survive. However, in general, given lung cancer patients' overall poor prognosis, it may be important for clinicians to consider appropriate palliative care to this group. For prostate cancer, where HRQOL was highest, the difference in scores for those with the most comorbid conditions who were diagnosed with cancer in the past year, to those with no comorbid conditions diagnosed more than 5 years ago, was still a wide margin at 10 points on the PCS and 4 points on the MCS. The additional disease burden in those with comorbid conditions has important implications for physical and psychological limitations in individuals with cancer. These results highlight the importance of assessing other chronic diseases when caring for cancer patients. Results also suggest that PCS and MCS scores are higher with increased time since diagnosis, although these results cannot conclusively determine longitudinal effects, given the cross-sectional nature of the data. These results underscore the need to specifically tease out the effects of comorbid conditions, time since diagnosis, and cancer-specific complications, when examining relationships between cancer and HRQOL in older adults.

Our results have a number of clinical implications. Among the various cancer types, kidney and lung patients reported the greatest number of comorbid conditions, and had major decrements in physical and mental health as compared with patients without cancer. These results may be due to several factors, including comorbid conditions, effectiveness of available treatment, complications of aggressive treatment, or the possibility of being diagnosed at a later stage (which is common among lung cancer patients). It also may be important to explore whether comorbidities are a consequence of cancer or

whether pre-existing comorbidities interact with cancer treatment, or both. For example, a recent randomized clinical trial of androgen-suppressing prostate cancer therapy showed an interaction between comorbidity and survival outcome. Overall, survival with the therapy was improved 80 percent. However, reduced mortality was seen only in males who had little or no comorbidity when they began treatment (D'Amico et al., 2008). These data highlight the importance of ensuring that patients' HRQOL needs are being addressed appropriately. Given the complexities of these relationships, it may be important to include a geriatric consultation or have geriatricians in the health care team to help manage the health care needs of older cancer patients (Gianni et al., 2001). This is especially important when designing supportive care interventions, particularly behavioral interventions such as those promoting physical activity. Clinicians need to be prepared to address the comorbidities that, combined with cancer, may significantly influence care and health outcomes.

The current effort extends previous research using MHOS data (Baker, Haffer, and Denniston, 2003; Ellis et al., 2004; Ko and Coons, 2005), by examining associations between several types of cancer and physical and mental health. Data from Baker and colleagues (2003) were based on the 1998 MHOS and data from Ko and Coons (2005) were based on the 2001 MHOS. Both suggested that cancer (grouped as one category) does not have nearly as strong associations with HRQOL scores as do other comorbid conditions. However, our data suggest that there are strong differences by type of cancer. In particular, lung cancer and NHL were both among the top five medical conditions associated with worse physical health, and lung cancer also had a strong negative relationship with mental health. Conversely, melanoma

had very little impact on either physical or mental health, which is not surprising given that melanoma treatment is often less aggressive, and the clinical course for early stage melanoma is more favorable than for other cancer types. Taken together, our results suggest that it is very important to examine the effects of cancer by particular cancer type.

Although these data have a number of strengths, they also have limitations. Due to the cross-sectional design of this analysis, we are unable to determine whether cancer patients are more likely to develop comorbid conditions after their diagnosis or whether they are pre-existing. Further, we cannot determine whether cancer patients are more likely to be diagnosed with comorbidities due to having more medical scrutiny or as a complication of cancer or its treatment. The MHOS does not provide information about the severity of comorbid conditions. It also only asks about 12 conditions and therefore does not capture such common conditions in the elderly as osteoporosis, benign prostatic hypertrophy, or dementia. Another limitation is that HRQOL was assessed using a generic measure, whereas a cancer-targeted instrument might have yielded information on symptoms particularly relevant for cancer patients. Further, we did not examine cancer treatment or staging information, and we did not have an objective measurement of comorbid conditions. However, data comparing MHOS survey items with medical records suggests that patients can provide reasonably good reports of their morbidity in survey questions (70 to 94 percent specificity and 65 to 85 percent sensitivity) (Miller et al., 2008).

The current analysis did not use a matched-design (such as the methods described by Reeve et al., 2008), but instead included relevant characteristics as covariates in the models. However,

there is evidence to suggest that adjusting for differences compared with matched propensity score designs often lead to the same conclusions (Rubin, 1979), particularly if groups are similarly distributed on the covariates (e.g. race, sex, age, etc.). Matched designs are more important when one group has a disproportionate representation of particular characteristics (e.g., one group is mostly Black, the other is mostly White; Rosenbaum and Rubin, 1985). In our sample, patients with and without cancer differed on a number of characteristics, but not dramatically. For example, cancer patients were slightly, but significantly older (approximately 1 year older on average) than patients without cancer. Finally, it is important to note that when examining time since cancer diagnosis as an important factor in predicting HRQOL, we are unable to tease apart a healthy survivor effect in which those who lived longer were healthier for a variety of unmeasured reasons. This is particularly true for lung cancer patients; 29 percent of lung cancer patients in this sample had survived for more than 5 years, while national survival rates are 14 percent. Thus, our findings may not generalize to those individuals with worse prognoses, although it is likely that longer survival would continue to be associated with better HRQOL. Future analyses should examine effects of cancer-specific variables, such as time since diagnosis as well as other medical comorbid conditions on survival.

Overall, this analysis adds to the existing cancer and HRQOL literature by comparing patients with several different cancer types (including many types that are less prevalent in the U.S. population) to patients without cancer. It was further able to demonstrate the importance of examining both the number of comorbidities and the time since a cancer diagnosis. These data clearly support the need for clinicians to assess

other medical comorbidities when treating cancer patients and developing supportive care interventions. Future research should extend these findings to more specific measures of HRQOL and examine other cancer-specific variables such as type, stage, and treatment.

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REFERENCES

- Ambs, A., Warren, J.L., Bellizzi, K.M., et al.: Overview of the SEER-Medical Health Outcomes Survey (MHOS) Linked Dataset. *Health Care Financing Review* 29(4): 5-22, Summer 2008.
- Baker, F., Haffer, S.C., and Denniston, M.: Health-Related Quality of Life of Cancer and Noncancer Patients in Medicare Managed Care. *Cancer* 97(3):674-681, February 2003.
- Bellizzi, K.M., and Rowland, J.H.: The Role of Comorbidity, Symptoms and Age in the Health of Older Survivors Following Treatment for Cancer. *Aging and Health* 3(5):625-635, October 2007.
- Bellizzi, K.M., Mustian, K.M., Palesh, O.G., et al.: Cancer Survivorship and Aging: Moving the Science Forward. *Cancer*. In press.
- Centers for Disease Control and Prevention: *The State of Aging and Health in America 2007*. 2007. Internet address: <http://www.cdc.gov/aging> (Accessed 2008.)
- Charlson, M.E., Pompei, P., Ales, K., et al.: A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. *Journal of Chronic Diseases* 40(5):373-383, January 1987.
- Cohen, J. A.: Power Primer. *Psychological Bulletin* 112:155-159, 1992.
- D'Amico, A.V., Chen, M., Renshaw, A.A., et al.: Androgen Suppression and Radiation vs. Radiation Alone for Prostate Cancer: A Randomized Trial *Journal of the American Medical Association* 299(3): 289-295, January 23, 2008.
- Ellis, B.H., Shannon, E.D., Cox, J.K., et al.: Chronic Conditions: Results of the Medicare Health Outcomes Survey, 1998-2000. *Health Care Financing Review* 25(4):75-91, Summer 2004.
- Extermann, M.: Interaction Between Comorbidity and Cancer. *Cancer Control* 14(1):13-22, January, 2007.
- Fouad, M.N., Mayo, C.P., Funkhouser, E.M., et al.: Comorbidity Independently Predicted Death in Older Prostate Cancer Patients, More of Whom Died with than from their Disease. *Journal of Clinical Epidemiology* 57(7):721-729, 2004.
- Gianni, W., Cacciafesta, M., Pietropaolo, M., et al.: Aging and Cancer: The Geriatrician's Point of View. *Critical Reviews in Oncology/Hematology* 39(3):307-311, September 2001.
- Guyatt, G., Walter, S., and Norman, G.: Measuring Change Over Time: Assessing the Usefulness of Evaluative Instruments. *Journal of Chronic Disability* 40(2):171-178, 1987.
- Hays, R.D., Farivar, S.S. and Liu, H.: Approaches and Recommendations for Estimating Minimally Important Differences for Health-Related Quality of Life Measures. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2(1):63-67, March 2004.
- Hays, R.D. and Morales, L.S.: The RAND-36 Measure of Health-related Quality of Life. *Annals of Medicine* 33:350-357, 2001.
- Hewitt, M., Rowland, J.H., and Yancik, R.: Cancer Survivors in the United States: Age, Health, and Disability. *Journal of Gerontology A: Biological Sciences and Medical Sciences* 58(1):82-91, January, 2003.
- Hodgson, N.A. and Given, C.W.: Determinants of Functional Recovery in Older Adults Surgically Treated for Cancer. *Cancer Nursing* 27(1):10-16, 2004.
- Institute of Medicine: *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*. In Adler, N.E. and Page, A.E.K. (eds.): The National Academies Press. Washington, DC. 2008.
- Janssen-Heijnen, M.L.G., Schipper, R.M., Razenberg, P.P.A., et al.: Prevalence of Co-Morbidity in Lung Cancer Patients and Its Relationship with Treatment: A Population-Based Study. *Lung Cancer* 21:105-113, 1998.
- Ko, Y. and Coons, S.J.: An Examination of Self-reported Chronic Conditions and Health Status in the 2001 Medicare Health Outcomes Survey. *Current Medical Research and Opinion* 21(11):1801-1808, November 2005.
- Koroukian, S.M., Murray, P., and Madigan, E.: Comorbidity, Disability, and Geriatric Syndromes in Elderly Cancer Patients Receiving Home Health Care. *Journal of Clinical Oncology* 24(15):2304-2310, 2006.
- Kosinski M., Zhao, S.Z., Dedhiya, S., et al.: Determining the Minimally Important Changes in Generic and Disease-Specific Health-Related

- Quality of Life Questionnaires in Clinical Trials of Rheumatoid Arthritis. *Arthritis & Rheumatism* 43(7):1478-1487, July 2000.
- Kurtz, M.E., Kurtz, J.C., Stommel, M., et al.: The Influence of Symptoms, Age, Comorbidity and Cancer Site on Physical Function and Mental Health of Geriatric Women Patients. *Women & Health* 29(3):1-12, 1999.
- Miller, D.R., Rogers, W.H., Kazis, L.E., et al.: Patients' Self-Report of Diseases in the Medicare Health Outcomes Survey Based on Comparisons with Linked Survey and Medical Data from the Veterans Health Administration. *Journal of Ambulatory Care Management* 31(2):161-177, 2008.
- Ogle, K.S., Swanson, G.M., Woods, N., et al.: Cancer and Comorbidity. *Cancer* 88:653-663, 2000.
- Piccirillo, J.F., Tierney, R.M., Costas, I., et al.: Prognostic Importance of Comorbidity in a Hospital-Based Cancer Registry. *Journal of the American Medical Association* 291(20):2441-2447, May 2004.
- Rao, A.V. and Demark-Wahnefried, W.: The Older Cancer Survivor. *Critical Reviews in Oncology/Hematology* 60:131-143, 2006.
- Reeve, B.R., Smith, A.W., Arora, N.K., et al.: Reducing Bias in Cancer Research: Application of Propensity Score Matching. *Health Care Financing Review* 29(4): 69-80, Summer 2008.
- Ries, L.A.G., Melbert, D., Krapcho, M., (eds.) et al.: *SEER Cancer Statistics Review, 1975-2004*. Internet address: http://seer.cancer.gov/csr/1975_2004/, Based on November 2006 SEER Data Submission, Posted to the SEER Web Site, 2007. (Accessed 2008.)
- Rosenbaum, P.R. and Rubin, D.B.: Constructing a Control Group Using Multivariate Matched Sampling Methods that Incorporate the Propensity Score. *The American Statistician* 39:33-38, 1985.
- Rubin, D.B.: Using Multivariate Matched Sampling and Regression Adjustment to Control Bias in Observational Studies. *Journal of the American Statistical Association* 74(366):318-324, June 1979.
- Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 13 Regs Public-Use, Nov 2005 Sub (1992-2003) - Linked To County Attributes - Total U.S., 1969-2003 Counties, National Cancer Institute. (Accessed March 27, 2007.)
- Ware, J.E. and Sherbourne, C.D.: The MOS 36-Item Short-Form Health Survey (SF 36®): I. Conceptual Framework and Item Selection. *Medical Care* 30(6): 473-483, June 1992.
- Ware, J.E., Jr, Snow, K.K., Kosinski, M., et al.: *SF-36 Health Survey Manual and Interpretation Guide*. The Health Institute. New England Medical Center. Boston, MA. 1993.
- Yancik, R.: Epidemiology of Cancer in the Elderly. Current Status and Projections for the Future. *Rays* 22:3-9, 1997.

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