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Comparison of stage at diagnosis of cancer in patients on dialysis versus the general population

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Abstract

Background—The frequent medical encounters in end-stage renal disease (ESRD) patients on dialysis may allow early detection of malignancies despite generally low rates of cancer screening in this population. It is therefore unclear whether dialysis patients are disadvantaged in terms of cancer diagnosis. To address this issue, we compared stage at diagnosis of cancer in a population-based sample of ESRD patients versus the general population.

Methods—The Surveillance, Epidemiology and End-Results (SEER)-Medicare database was used to identify ESRD patients with incident cancers from 1992 through 1999. Modified Poisson regression models were used to predict non-localized stage of cancer at diagnosis in ESRD patients versus the general population adjusting for demographics, cancer site, region, year of diagnosis and comorbidity. Two general population comparisons were used: standardized SEER public use data and Medicare non-ESRD controls matched 3:1 to ESRD patients.

Results—A total of 1629 ESRD patients with incident cancer were identified. Overall, the likelihood of non-localized stage at diagnosis was not significantly different for ESRD patients versus the standardized SEER general population (RR 0.90; 95%CI: 0.81-1.01) or matched Medicare controls (RR 0.97; 95%CI: 0.89-1.07). When analyzed by cancer site, colorectal cancers were significantly more likely to be diagnosed earlier in the ESRD group, whereas prostate cancers were significantly more likely to be diagnosed at a later stage.

Conclusion—In conclusion, this study demonstrates that, with the notable exception of prostate cancer, ESRD patients are not more likely to present with later stage malignancies compared to the general population.

INTRODUCTION

Screening for cancer in end-stage renal disease (ESRD) patients on dialysis remains controversial (1-3). Despite some evidence supporting an increased risk of malignancy in patients on chronic dialysis (4), the issue of cancer is generally overshadowed by the overwhelming cardiovascular mortality (5,6). A cost-effectiveness analysis suggested that a general cancer screening program in this population would be of minimal value, adding less than 5 days of life saved per person under the most optimistic assumptions (7). Indeed, population-based assessments suggest that cancer screening does occur less frequently in dialysis patients versus the general population (8,9).

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Some authors, however, have expressed concern over the low rates of cancer screening in the chronic dialysis population, and suggest that the decision to screen may need to be individualized, with consideration given to those patients with a reasonable life expectancy (2,3,8). In addition, the issue of cancer may become more relevant in dialysis patients with the progressive aging of the population (10), and trends showing improvement in cardiovascular outcomes in recent years (11).

Nevertheless, the frequent medical encounters that occur by virtue of the dialysis procedure may allow for early detection of malignancies even in the absence of formal screening for cancer. It is therefore unclear whether chronic dialysis patients are disadvantaged in terms of cancer diagnosis. To address this issue, we compared stage at diagnosis of cancer in a population-based sample of chronic dialysis patients versus the general population.

METHODS

Data Sources

This study used the linked Surveillance, Epidemiology and End-Results (SEER)-Medicare database (12). The SEER program, sponsored by the National Cancer Institute, consists of a group of population-based tumor registries in selected geographic areas covering approximately 14% of the US population. Medicare is a federal program that covers health services for patients on the basis of age (65 years and older), disability or need for renal replacement therapy. It provides data in the form of claims submitted by providers for reimbursement that include information on diagnoses (for justification of services rendered) and the service, testing or procedure carried out. The information in the two programs was merged using an algorithm involving a match of social security number, name, sex, and date of birth, as described elsewhere (13). The version of the SEER-Medicare database used for this study contained Medicare claims through 2001 and SEER cancer cases through 1999. Additional information on cancer in the general population was available from the SEER public use data files (14).

Study Subjects

Among patients in the SEER-Medicare database with an incident cancer from January 1, 1992 through December 31, 1999, subjects with ESRD requiring dialysis were identified. First, patients with ESRD as their original source of Medicare entitlement (generally those younger than age 65) were identified directly from the Medicare entitlement indicator code. Second, for those whose original entitlement for Medicare was not due to ESRD (generally those 65 years and older), patients were identified on the basis of an outpatient Medicare claim for a dialysis procedure (any of Current Procedural Terminology, 4th edition [CPT-4] codes 90918-90925, 90935-90937, 90945-90947, 99559, 90951-90958, 90966-90985, 90988-90991, 90994; or revenue center codes 80X, 82X, 83X, 84X, 85X, 86X, 87X; or International Classification of Diseases, ninth revision [ICD-9] procedure codes 39.95, 54.98) combined with a diagnosis of chronic renal failure (any of ICD-9 codes 582, 585, 586, 587, 403, 404, 250.4). Patients whose cancer was diagnosed prior to their designation of ESRD or after a renal transplant (identified from ICD-9 procedure code 55.69) were excluded. Cancer sites with less than 100 cases were excluded.

Study Variables

Demographics such as age at diagnosis, gender, race, marital status, date of cancer diagnosis and geographic region of residence were available from the SEER-Medicare data files. In addition, the SEER cancer files provided information on the site of cancer, and the stage at diagnosis. Cancer staging for this study was based on the SEER “historic” staging system which is divided as in-situ, localized (confined to organ), regional (extension beyond organ), or distant

(invasion of adjacent organs or distant metastases) spread (15). For the purposes of analysis, the staging variable was dichotomized as localized (in-situ or localized) versus non-localized (regional or distant). This cut-off was chosen for clinical relevance because for most malignancies, localized tumors are potentially curable. However, choosing the stage cut-off as non-distant (in-situ, localized or regional) versus distant did not alter the study conclusions. For lymphomas, "localized" stage equated to nodal disease confined to one side of the diaphragm, whereas "non-localized" stage equated to disease involving both sides of the diaphragm or extra-nodal spread. For prostate cancer, the SEER staging system combines localized and regional cases into one stage, so it was analyzed separately, as non-distant versus distant spread. Socio-economic status in the form of income was not available at the individual level so a surrogate value was used based on percent of residents living below the poverty level in the census tract of residence. Comorbidity was assessed using a modified form of the Charlson comorbidity index developed for use with Medicare claims (16,17). The public use SEER data contained information on age, gender, race, cancer site, stage, geographic region and year of diagnosis.

Statistical Analyses

The observed rates of ESRD patients diagnosed at a non-localized stage were calculated for each cancer site. Comparisons were made to the general population in two ways. First, standardized rates of stage at diagnosis in the general population were estimated by applying the appropriate cancer site-, age-, sex-, race-, year-, and region-specific rates from public use SEER data to the numbers of ESRD patients within the appropriate strata. These data were entered into a modified Poisson regression model (which allows for valid estimation of relative risks) (18) with the dependent variable being non-localized stage at diagnosis. Relative risks (RR) with 95% confidence intervals (CI) for non-localized stage at diagnosis for ESRD patients versus general population were calculated overall and for each cancer site.

The second general population comparison involved use of non-ESRD patients in the SEER-Medicare database as a reference group. This approach was therefore limited to older patients but had the advantage of eliminating the influence of health insurance coverage (since all patients were Medicare eligible) and allowing adjustment of other potential confounders influencing stage at diagnosis such as marital status, socio-economic status and comorbidity. In order to evaluate comorbidity (from claims in the 12 months preceding diagnosis of cancer), these analyses were limited to patients aged 66 years and older, enrolled in Medicare part A and B and not a member of a Health Maintenance Organization (HMO) for the 12 months before cancer diagnosis. Three non-ESRD patients were selected by matching at cancer site, age at diagnosis (± 5 years), gender, race, and year of diagnosis for each ESRD patient. Non-ESRD patients were selected randomly when greater than three were identified, whereas all were selected if three or less matching patients were identified (for 98.5% of ESRD patients, 3 controls were identified). The modified Poisson regression approach was again used to build a model predicting stage at diagnosis of cancer by ESRD status.

Analyses were performed with the software packages SAS version 9.1 (Cary, NC). All tests of statistical significance were two-sided, with *P* values of less than 0.05 being considered statistically significant. The study protocol was approved by the local institutional review board at the University of Texas Medical Branch at Galveston.

RESULTS

A total of 1629 ESRD patients with incident cancer were identified in the SEER-Medicare database from 1992 through 1999. Table 1 presents their demographic characteristics and distribution of cancer sites. The overall age of the group at diagnosis was 67.4 years, with roughly two thirds of patients aged 65 years or older. For patients aged 65 years or older, the

most common cancer sites were the major solid organ malignancies: lung, colorectal, prostate and breast. In contrast, in younger patients, renal cell cancers were especially frequent, with kidney being the second most common cancer site after lung.

Table 2 presents data based on modified Poisson regression models comparing the likelihood of a non-localized stage of cancer at diagnosis in the ESRD group to standardized general population data from SEER. Relative risks greater than 1 suggest a later stage at diagnosis in ESRD patients, whereas ratios less than 1 suggest an earlier stage at diagnosis. Overall, there was no significant difference in stage at diagnosis for ESRD patients versus the general population when all cancer sites were examined simultaneously. When the analysis was stratified by individual cancer sites, colorectal cancers were significantly more likely to be diagnosed at an earlier stage in ESRD patients, whereas prostate cancers were significantly more likely to be diagnosed at a later stage compared to the general population. This pattern was similar when the analyses were divided into patients younger than 65 and those 65 and older, although none of the results achieved statistical significance. In the younger age group, there was a trend towards earlier stage at diagnosis in the ESRD group for kidney cancers (RR 0.64, 95%CI: 0.38-1.06, p = 0.08). No substantial differences were noted when the analyses were stratified by race or sex (data not shown).

Table 3 presents data based on modified Poisson regression models comparing likelihood of a non-localized stage of cancer at diagnosis in the ESRD group to matched non-ESRD Medicare controls, adjusted for comorbidity, income and marital status. This analysis was limited to Medicare eligible patients aged 66 years and older. Similar to the analysis presented in Table 2, there was no significant difference in stage between the ESRD and non-ESRD group when all cancer sites were analyzed together. Colorectal cancers were again significantly more likely to be diagnosed earlier in the ESRD group, whereas prostate cancers were significantly more likely to be diagnosed at a later stage. Compared to the analysis of patients aged 65 years and older in Table 2, the odds ratios for lymphoma, and lung, kidney and breast cancers increased, but only kidney cancers were diagnosed at a significantly later stage in the ESRD group (RR 1.36, 95%CI: 1.00-1.85, p = 0.048).

Based on the consistent finding of significant differences in stage at diagnosis for prostate and colorectal cancers, additional analyses were performed to examine whether differences between the ESRD and non-ESRD groups existed in frequency of medical work-up relevant to these malignancies. Medicare claims were searched to determine the rates of prostate specific antigen (PSA) testing (any of CPT-4 codes 84152-84154, Healthcare Common Procedure Coding System [HCPCS] code G0103) and lower gastrointestinal endoscopy (any of ICD-9 procedure codes 45.23, 45.24, CPT-4 codes 45330, 45355, 45378, HCPCS codes G0104, G0105) in the prostate cancer and colorectal cancer groups, respectively, during the period 12 to 24 months prior to diagnosis. This period was chosen to avoid simply identifying the tests that actually led to the diagnosis of the cancer. PSA testing was significantly less likely (Odds ratio 0.59, 95%CI: 0.36-0.96) whereas lower endoscopy (colonoscopy or flexible sigmoidoscopy) was more likely (Odds ratio 3.65, 95%CI: 1.21-11.03) in the ESRD versus the non-ESRD group.

DISCUSSION

This is the first study, to our knowledge, that systematically compares stage at diagnosis of cancer in the ESRD versus the general population. Despite low rates of cancer screening in ESRD patients on dialysis, this study suggests that, with some exceptions, they are not more likely to be diagnosed with a later stage of cancer in comparison to the general population. This may occur because of a number of distinct qualities of the ESRD population. First, virtually all ESRD patients qualify for health insurance through Medicare. Health insurance

availability is an important predictor of cancer stage at diagnosis (19). In our study, this is supported by the fact that ESRD patients were generally less advantaged in terms of stage at diagnosis (i.e., relative risks for non-localized stage were higher) when the comparison group included only Medicare eligible patients, versus the public SEER data (which includes patients without health insurance). Second, contact with medical care is frequent by virtue of the dialysis procedure. The typical hemodialysis patient may be seen as much as once a week by a physician. A higher frequency of outpatient physician visits for routine care has been associated with earlier stage at diagnosis for breast cancer (20). Third, a related point is that medical work-up for a number of health issues is frequent in the ESRD patient, perhaps increasing the possibility of incidental, early stage cancer diagnoses. This may be of particular relevance for malignancies for which no screening modality exists. For example, the high incidence of thyroid malignancies in ESRD patients has been attributed in part to the frequent work-up of parathyroid disorders (21). Finally, some dialysis patients may receive intensive screening activities as part of a work-up prior to renal transplantation. However, since no information on waitlisting for transplant was available, this issue could not be examined directly as part of this study.

A striking finding of this study was that ESRD patients were about twice as likely to present with a distant, and therefore incurable, stage at diagnosis of prostate cancer. This may be in part due to lower use of PSA screening in the ESRD population, demonstrated both in this study and in previous work (8,9). In addition, the absence of urinary output may hinder early diagnosis on the basis of urinary tract symptoms (22). Despite the poor outcome in distant disease, it is still unclear whether PSA screening reduces mortality in the general population (23). One of the main problems with PSA screening is the frequent detection of early stage disease of no clinical significance due to the competing risk of death from other causes (24). This issue is of particular relevance given the substantial morbidity and mortality in the dialysis population. It may therefore be prudent to limit consideration of PSA screening to dialysis patients with a life expectancy of at least 10 years, and ensure an adequate discussion of the risks, benefits and uncertainties (25).

The finding that ESRD patients were diagnosed with earlier stage colorectal cancers may relate to more frequent gastrointestinal work-up in this population. This is supported by additional analyses demonstrating that ESRD patients were more likely to receive colonoscopy or flexible sigmoidoscopy in the 12 to 24 months prior to diagnosis of cancer. A number of factors may have contributed to this finding. Anemia is extremely common in dialysis patients and may have prompted work-up for sources of gastrointestinal blood loss (26). Uremic platelet dysfunction combined with anticoagulation given during hemodialysis results in a bleeding diathesis that may bring gastrointestinal lesions to attention earlier (27). For instance, dialysis patients are more likely to have positive stool guaiac tests than non-uremic controls (28). Finally, diagnostic evaluations for gastrointestinal diseases especially common in dialysis patients, such as angiodysplasia or constipation, may lead to incidental identification of malignant lesions (29).

A number of studies have reported differences in the incidence of various cancers between the dialysis and general populations (4,30,31). Although these differences may relate to the true risks of malignancy in the setting of dialysis or uremia, they could also result from differences in surveillance for cancers. For example, if the later stage of prostate cancer in dialysis patients noted in our study was due to reduced surveillance, a lower incidence of prostate cancer would be expected. Examining this issue we did find that the incidence of prostate cancer was significantly lower (standardized incidence ratio [SIR] of 0.47 [95%CI:0.43 -0.53]) in the dialysis versus the general population, consistent with previously published findings (4,30). Similarly, if the earlier stage of colorectal cancer in dialysis patients noted in our study was due to increased surveillance, a higher incidence of colorectal cancer would be expected.

However, we did not find a significant difference in incidence of colorectal cancer (SIR of 0.96 [95%CI:0.84 - 1.09]), although other larger studies have noted a modest increase in the dialysis population (4,30).

This study has important limitations. It was limited by power due to the relatively small sample sizes. The confidence intervals for several of the individual cancer sites were therefore too wide to allow any meaningful conclusions or stratified analyses. Nevertheless, this study carries the advantage that it is population-based and therefore likely to be representative of actual practice. Also, due to limitations of sample size and a Medicare claims-based approach, not all potentially relevant variables (e.g. digital rectal exams, routine physical exams) were available or could be entered into the models. However, the models were adjusted for a select number of variables previously shown to be strongly predictive of cancer stage at diagnosis, such as marital and socio-economic status. Another limitation has to do with potential biases related to the staging process in the tumor registries. Since information from operative reports are incorporated into determination of staging, patients undergoing surgery for their cancers are more likely to be reported as having later stage tumors due to detection of disease extension not evident by clinical or radiological assessments (15). This could have biased the results toward earlier stages at diagnosis reported for ESRD patients if they systematically underwent surgery for their cancers less often. However, with the exception of prostate cancer, surgery is generally considered standard of care for most localized, solid organ malignancies (32). When we examined the SEER data, rates of surgery for localized breast, kidney, and colorectal cancers were greater than 90% for both the ESRD and standardized general populations. Rates of surgery for localized lung cancers were lower in ESRD patients at 43% versus 62% in the standardized general population, likely explained by a greater number of comorbidities in the ESRD group (33). However, the adjustment for comorbidity in the analyses performed in Table 3 would have mitigated the difference in rates of surgery and its impact on assessment of stage at diagnosis.

In conclusion, this study demonstrates that, with the notable exception of prostate cancer, ESRD patients are not more likely to present with later stage malignancies despite generally lower rates of screening compared to the general population. This may occur due to the higher frequency of physician visits or more intensive medical work-ups in patients on dialysis.

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Table 1

Characteristics of end-stage renal disease patients with cancer

Characteristics	Category	Overall		Patients aged < 65 years		Patients aged ≥65 years	
		n	%	n	%	n	%
Total		1629		557		1072	
Age at diagnosis(years)	< 55	237	14.5%	237	42.5%	-	-
	55 - 64	320	19.6%	320	57.5%	-	-
	65 - 74	579	35.5%	-	-	579	54.0%
	≥75	493	30.3%	-	-	493	46.0%
	Mean±SD		67.4±11.8		54.3±8.4		74.3±6.2
Gender	Male	935	57.4%	341	61.2%	594	55.4%
	Female	694	42.6%	216	38.8%	478	44.6%
Race	White	808	49.6%	206	37.0%	602	56.2%
	Black	510	31.3%	237	42.5%	273	25.5%
	Other	311	19.1%	114	20.5%	197	18.4%
Year of Diagnosis	1992-93	300	18.4%	87	15.6%	213	19.9%
	1994-95	429	26.3%	150	26.9%	279	26.0%
	1996-97	416	25.5%	148	26.6%	268	25.0%
	1998-99	484	29.7%	172	30.9%	312	29.1%
Geographic Region	Northeast	182	11.2%	56	10.1%	126	11.8%
	Midwest	405	24.9%	129	23.2%	276	25.7%
	South	198	12.2%	100	18.0%	98	9.1%
	West	844	51.8%	272	48.8%	572	53.4%
Cancer Site	Breast	259	15.9%	90	16.2%	169	15.8%
	Bladder	111	6.8%	34	6.1%	77	7.2%
	Colorectal	325	20.0%	94	16.9%	231	21.5%
	Kidney	167	10.3%	100	18.0%	67	6.3%
	Lung	404	24.8%	104	18.7%	300	28.0%
	Non-Hodgkin Lymphoma	102	6.3%	55	9.9%	47	4.4%
	Prostate	261	16.0%	80	14.4%	181	16.9%

Table 2

Likelihood of non-localized stage of cancer at diagnosis in the ESRD versus standardized general population

Cancer Site	Overall Group			Patients Aged < 65 years			Patients Aged ≥65 years		
	ESRD	General Population[a]	RR (95%CI)[b]	ESRD	General Population[a]	RR (95%CI)[c]	ESRD	General Population[a]	RR (95%CI)[d]
All[e]	45.5%	50.0%	0.90 (0.81,1.01)	44.0%	52.2%	0.88 (0.73,1.06)	46.2%	48.8%	0.92 (0.80,1.05)
Breast	32.5%	28.8%	1.13 (0.82,1.54)	33.3%	33.1%	1.01 (0.61,1.67)	32.0%	26.5%	1.20 (0.81,1.79)
Bladder	28.8%	23.8%	1.21 (0.72,2.03)	32.3%	20.9%	1.55 (0.60,3.97)	27.3%	25.0%	1.09 (0.59,2.01)
Colorectal	40.9%	52.6%	0.78 (0.62,0.98)	42.6%	55.1%	0.77 (0.51,1.17)	40.3%	51.3%	0.78 (0.60,1.02)
Kidney	33.6%	40.4%	0.83 (0.58,1.18)	24.0%	37.5%	0.64 (0.38,1.06)	47.8%	43.9%	1.08 (0.65,1.78)
Lung	62.9%	71.4%	0.88 (0.74,1.04)	75.4%	77.3%	0.85 (0.61,1.17)	62.0%	69.4%	0.89 (0.73,1.09)
Lymphoma	61.7%	58.0%	1.06 (0.75,1.52)	67.3%	58.0%	1.16 (0.72,1.87)	55.3%	58.1%	0.95 (0.56,1.63)
Prostate[f]	12.6%	6.7%	1.87 (1.05,3.33)	10.0%	5.1%	1.94 (0.59,6.37)	13.8%	7.4%	1.85 (0.95,3.58)

ESRD = end-stage renal disease

[a] From public use Surveillance, Epidemiology and End-Results registry data standardized to cancer site, age, sex, race, year, and region strata from the ESRD group

[b] From a modified Poisson regression model predicting non-localized stage at diagnosis, with independent variables including ESRD status, age at diagnosis, race, gender, SEER geographic region of residence, year of diagnosis and cancer site

[c] From a modified Poisson regression model similar to the overall group but limited to patients aged less than 65 years at diagnosis

[d] From a modified Poisson regression model similar to the overall group but limited to patients aged 65 years and older at diagnosis

[e] Excluding prostate cancer

[f] Outcome is likelihood of distant stage at diagnosis

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Table 3

Likelihood of a non-localized stage of cancer at diagnosis in the ESRD versus matched non-ESRD Medicare population

Cancer Site	ESRD (total n[a])	Non-ESRD[b]	RR (95%CI)[c]
All[d]	45.9% (728)	49.6%	0.97 (0.89,1.07)
Breast	30.7% (140)	24.1%	1.35 (0.99,1.82)
Bladder	25.7% (70)	26.4%	1.02 (0.64,1.63)
Colorectal	39.0% (195)	50.9%	0.81 (0.66,0.98)
Kidney	55.8% (52)	42.2%	1.36 (1.00,1.85)
Lung	62.1% (240)	70.6%	0.92 (0.82,1.04)
Lymphoma	61.3% (31)	58.1%	1.09 (0.78,1.51)
Prostate[e]	13.7% (139)	6.5%	2.36 (1.35,4.13)

ESRD = end-stage renal disease

[a] Limited to patients aged 66 years and older, enrolled in Medicare part A and B and not a member of an health maintenance organization for the 12 months before cancer diagnosis

[b] Patients with cancer in the Surveillance, Epidemiology and End-Results – Medicare database not meeting criteria for ESRD status. Three were selected randomly for each ESRD patient by matching at cancer site, age at diagnosis (± 5 years), gender, race, and year of diagnosis

[c] From a modified Poisson regression model predicting non-localized stage at diagnosis, with independent variables including ESRD status, age at diagnosis, race, gender, SEER geographic region of residence, year of diagnosis, comorbidity index, marital status, percent of residents below poverty level in census tract of residence, and cancer site

[d] Excluding prostate cancer

[e] Outcome is likelihood of distant stage at diagnosis