Identification of Second Primary Malignancies (SPM) in Men With Castration-Resistant Prostate Cancer (CRPC) in SEER-Medicare Data (Abstract #2256)

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BACKGROUND

- Population-based epidemiological studies have been conducted to estimate the incidence rates of SPM (newly detected malignancies) among cancer survivors with prostate cancer. However, such data in patients with CRPC are limited. We conducted a retrospective cohort study of the SPM incidence among men with CRPC in the United States (US).

OBJECTIVES

- To estimate the incidence of SPM, evaluate the effect of varying the criteria for defining SPM, and explore case confirmation in Medicare claims profiles.

METHODS

Data Source

- The Surveillance, Epidemiology, and End Results (SEER)–Medicare linked database, which is administered by the US National Cancer Institute (NCI), links two sets of databases using a unique case identification number.
  - Combines data from the SEER Program (beginning in 1991, through 2011 for this study), which collects population-based cancer registry data covering approximately 30% of the US population,[1] with data from Medicare, the US federal health insurance program primarily for people aged 65 years or older
  - The term "SEER-Medicare data" refers to a series of files: one file contains SEER data, while the other files contain Medicare claims data for specific types of services (e.g., hospital, physician, or outpatient visits). Patient data are linked across the various files using the unique SEER case identification number.[2]
  - Contains detailed information for each primary cancer and individual, including the initial diagnosis and date of death
- US federal insurance data have been used for decades to supplement SEER data in identifying cancer in older Americans, but results depend on criteria used to define cases.[3]

Study Period

- The study period was 1 January 2000 through the latest year of available Medicare data (2013).

Study Design and Subjects

- This was a retrospective, observational cohort study of men in the US.
- Castration-resistant prostate cancer (definition in clinical practice):
  - Advanced prostate cancer progression despite medical or surgical castration. Key defining factors usually include castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either[4]:
    (1) Biochemical progression—three consecutive rises of prostate-specific antigen (PSA), 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL, or
    (2) Radiological progression—the appearance of two or more bone lesions on bone scan or enlargement of a soft-tissue lesion using Response Evaluation Criteria in Solid Tumors (RECIST).
- However, information regarding serum testosterone levels, PSA measurements, and results of bone imaging studies are not available in Medicare claims data. Therefore, the present study used a pragmatic approach to defining CRPC based on second-line treatments administered after surgical or medical castration to indicate that progression had occurred despite castration.
- Specifically, SEER data were used initially to identify all men in the study population diagnosed with prostate cancer. Algorithms specifying orchiectomy that were created for a previous study[5] were used to identify surgical castration (bilateral orchiectomy). A list of drugs described in the American Urological Association Guidelines[6] was adapted to identify medical castration (androgen deprivation therapy). Use of second-line systemic treatments indicated castrate resistance.[4,6,7]
- Inclusion criteria:
  - Primary site code of prostate cancer (International Classification of Diseases for Oncology, Third Edition [ICD-O-3] topography code C61.9) with behavior code "/3" (malignant) in SEER data.
  - Surgical castration or androgen deprivation therapy after prostate cancer diagnosis. Androgen deprivation therapy was identified by the use of any of the following drugs: abarelix, bicalutamide, buserelin, cyproterone, degarelix, diethylstilbestrol, estramustine, flutamide, gonadorelin, goserelin, histrelin, leuprolide, medroxyprogesterone, megestrol, nafarelin, nilutamide, polyestradiol, or triptorelin.
  - Evidence that the prostate cancer became resistant to surgical castration or androgen deprivation therapy, as indicated by starting one of the following second-line systemic therapies: abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, or sipuleucel-T (defines cohort entry date).
  - Aged 65 years or older on the cohort entry date.
  - Medicare Parts A and B enrolment for at least 1 year before cohort entry and continuously between date of initial prostate cancer diagnosis and cohort entry date.
- Exclusion criteria: see Table 1.

Outcome

- SPM were ascertained using both SEER data and Medicare data.
- The strategy of using one inpatient or two outpatient or physician claims was selected as the main analysis (base criterion) because it is consistent with methodology used by the CMS Chronic Conditions Data Warehouse.[8]
- Other criteria used various combinations of SEER and Medicare data.

Analysis

- Two study epidemiologists manually reviewed Medicare claims profiles for cases of the three most common SPM identified by the base criterion to understand whether these had been correctly classified as SPM.

RESULTS

- NCI supplied data on 564,491 individuals diagnosed with prostate cancer since 2000. Applying the inclusion and exclusion criteria resulted in a final cohort of 2,234 patients (see Table 1). Table 2 through Table 5 describe the demographic and clinical characteristics and treatments for the study population.
- The base criterion (1 record in SEER or 1 inpatient claim in Medicare or 2 outpatient or physician claims) identified 172 SPM among the 2,234 men with CRPC, of which only 20 were identified by SEER data (see Table 6). The main study results have been previously published.[9]
- Table 6 shows the varied requirements for defining SPM and the resulting number of cases and corresponding incidence rate for each. The criteria range from most sensitive to most stringent from the top to the bottom row of the table. The least restrictive criterion (a single claim in any Medicare file or a SEER diagnosis) identified 545 SPM.
- Based on varying criteria, the estimated rates of SPM per 1,000 person-years ranged from 9 (95% confidence interval [CI], 6-14) to 213 (95% CI, 196-232). Using the base criterion, the crude incidence rate was 59 (95% CI, 50-68) (see Table 6).
- We also estimated incidence rates by type of SPM. We categorized types of SPM by clinical criteria and to comply with reporting limits set by the SEER-Medicare Data Use Agreement (which prohibits reporting cell counts less than 11) (see Table 7).
- Given the substantial variability in the estimated rates of SPM based on the criteria used, we reviewed individual patient and Medicare claims files for the three most common SPM, identified by the base criterion (lung/bronchus, urinary bladder, and colon/rectum; n = 72).
- The majority of the 72 cases did not contain specific enough evidence to confirm a histologically distinct SPM (as opposed to spread of prostate cancer to other organs). Because there was no "gold standard" on which to base a confirmation, we counted the frequency of unique dates on which a diagnosis for the specific SPM was recorded.
- Overall, SPM diagnoses were recorded a median of 3 times per patient in Medicare data (range, 1-50). On average, SPM cases found in SEER had the diagnosis listed about twice as often in Medicare data as SPM cases not found in SEER (mean, 11.8 vs. 6.0) (ratio, 2.0; 95% CI, 1.7-2.5).

Table 1. Cohort Selection

Reason for Exclusion	Number of Patients (%)	Remaining Sample
Initial sample of prostate cancer cases from SEER-Medicare	564,491 (100)	564,491
No record of surgical or medical castration	383,713 (67.98)	180,778
No record of second-line systemic therapy[a] after castration date	168,388 (29.83)	12,390
Castration was on or before prostate cancer diagnosis date	376 (0.07)	12,014
Diagnosis of any cancer other than prostate cancer or non-melanoma skin cancer on or before potential cohort entry date	5,543 (0.98)	6,471
Diagnostic code for exclusionary metastases (197X or 198X except for 198.2-skin or 198.5-bone) on or before potential cohort entry date	1,767 (0.31)	4,704
Not aged at least 65 years on potential cohort entry date	246 (0.04)	4,458
Not continuously enrolled in both Parts A and B Medicare coverage between the earlier of (1) 12 months before cohort entry or (2) the month of prostate cancer diagnosis and cohort entry date	1,293 (0.23)	3,165
Enrolled in HMO either (1) in year before potential cohort entry date or (2) at some time between diagnosis date of initial prostate cancer identified in SEER and potential cohort entry date	931 (0.16)	2,234
Claim for treatment with Xofigo (radium-223 dichloride) on or before potential cohort entry date	0 (0.00)	2,234

HMO = health maintenance organization.
[a] Abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, or sipuleucel-T.

Table 2. Demographic Characteristics of Study Cohort (N = 2,234)

Variable	Number of Patients (%)
Age at cohort entry, years	
Mean (SD)	76.6 (6.2)
Age group	
65-69	297 (13.3)
70-74	625 (28.0)
75-79	595 (26.6)
80-84	451 (20.2)
85+	266 (11.9)
Race	
White	1,867 (83.6)
Black	218 (9.8)
Asian	46 (2.1)
Hispanic	48 (2.1)
Other or unknown[a]	55 (2.5)

[a]Categories were combined to avoid reporting a count of < 11.

Table 3. Clinical Characteristics of Study Cohort (N = 2,234)

Variable	Number of Patients (%)
Characteristics at initial prostate cancer diagnosis	
Stage (derived group)[a]	
Stage I or II[b]	543 (24.3)
Stage III	107 (4.8)
Stage IV	583 (26.1)
Unknown	1,001 (44.8)
Characteristics on or before cohort entry date	
Comorbidities[c]	
Chronic pulmonary disease	947 (42.4)
Diabetes without chronic complications	920 (41.2)
Peripheral vascular disease	830 (37.2)
Cerebrovascular disease	681 (30.5)
Congestive heart failure	636 (28.5)
Mild liver disease	512 (22.9)
Renal disease	487 (21.8)
Myocardial infarction	359 (16.1)
Diabetes with chronic complications	273 (12.2)
Rheumatic disease	183 (8.2)
Peptic ulcer disease	171 (7.7)
Paraplegia and hemiplegia	87 (3.9)
Dementia	83 (3.7)
Moderate or severe liver disease	18 (0.8)
AIDS/HIV	< 11
Metastases[d]	
Lymph node	296 (13.2)
Bone	1,797 (80.4)
Bone-directed therapy[e]	1,326 (59.4)
Either bone metastases or bone-directed therapy	1,887 (84.5)
Time from initial diagnosis to development of CRPC	
Mean (SD), months	42.1 (32.6)
Distribution	
< 6 months	89 (4.0)
6 months to 1 year	251 (11.2)
> 1 to 1.5 years	279 (12.5)
> 1.5 to 2 years	223 (10.0)
> 2 years	1,392 (62.3)

HIV = human immunodeficiency virus; NOS = not otherwise specified; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
[a] Stage according to the AJCC Staging Manual, Sixth Edition.[10]
[b] Categories were combined to avoid reporting a count of < 11.
[c] Individual patients can have multiple comorbidities; thus, the sum of all comorbidities adds up to more than 100%.
[d] Recorded anytime between initial date of prostate cancer diagnosis and 30 days after the cohort entry date.

Table 4. Treatments Reported for Study Cohort (N = 2,234)

Variable	Number of Patients (%)
Castration method	
Surgical	52 (2.3)
Medical	2,106 (94.3)
Surgical and medical	76 (3.4)
Treatment recorded after cohort entry date (from Medicare)[a]	
Chemotherapy	2,121 (94.9)
Radiation therapy	725 (32.5)
Radiopharmaceuticals (strontium-89 or samarium-153)	103 (4.6)

[a] The percentages add to > 100 because patients could be in more than one treatment category.

Table 5. Type of Second-Line Therapy

Type of Second-Line Therapy	n	%
Docetaxel	1,697	76.0
Abiraterone acetate	215	9.6
Sipuleucel-T	191	8.5
Mitoxantrone	86	3.8
Enzalutamide	30	1.3
Cabazitaxel	15	0.7
Total	**2,234**	**100.0**

Table 6. Second Primary Malignancies Identified in SEER and Medicare Using Varying Criteria

	Requirements							Results		
		Medicare								
Criterion	SEER	MedPAR (Inpatient)[a]	NCH (Physician)[b]	Outpatient[c]	HHA[d]	Hospice[e]	DME[f]	Cases Identified by Algorithm	Follow-up Years	Rate Per 1,000 Person-Years (95% CI)
1	1	1	1	1	1	1	1	545	2,553	213 (196-232)
2	1	1	1	1	—	1	—	526	2,564	205 (188-223)
3	1	1	1	1	—	—	—	521	2,564	203 (186-221)
4	1	1	1	2	2	2	2	475	2,618	181 (165-199)
5	1	1	1	2	—	2	—	463	2,625	176 (161-193)
6	1	1	1	2	—	—	—	461	2,626	176 (160-192)
7	1	1	1	—	—	—	—	454	2,632	172 (157-189)
8	1	1	2	2	2	2	2	193	2,910	66 (57-76)
9	1	1	2	2	—	2	—	177	2,921	61 (52-70)
10	**1**	**1**	**2**	**2**	**—**	**—**	**—**	**172**	**2,922**	**59 (50-68)**
11	1	1	2	—	—	—	—	159	2,934	54 (46-63)
12	1	1	—	—	—	—	—	60	3,051	20 (15-25)
13	**1**	**—**	**—**	**—**	**—**	**—**	**—**	**20**	**2,153**	**9 (6-14)**

DME = durable medical equipment; HHA = home health agency; MedPAR = Medicare Provider and Analysis Review; NCH = national claims history.
1: represents an SPM recorded among their diagnoses. 2: represents two SPM recorded among their diagnoses. Criterion 10 was chosen for this study, which required 1 record in SEER, 1 inpatient claim in Medicare, 2 physician claims in Medicare, or 2 outpatient claims in Medicare. Number of diagnoses, on different dates, recorded in any data file listed for a given criterion.
See handout for notes a-f.

DISCUSSION AND CONCLUSIONS

- Most SPM were identified only in Medicare data. We observed variability in SPM incidence rates depending on choice of requirements for their ascertainment.
- Very few cases of SPM in our study (20) were found by using SEER data alone. Although we have no direct evidence to understand the reasons for this number being so low in relation to the number of cases found using both SEER and Medicare data, we can speculate about some possibilities:
  - SPM may be underreported to cancer registries, particularly for patients who are diagnosed with an SPM on a clinical basis (without pathological confirmation), perhaps because they have advanced prostate cancer or other comorbidities that prompt a less aggressive approach to diagnosis.
  - The SEER data have a shorter follow-up time than the Medicare data (by about 2 years); however, judging from the number of SPM identified in the last 2 years of the study (n = 42), it can be estimated that this would account for at most approximately 25% of the case deficit in SEER data.
  - Patients may have moved out of a SEER reporting region and therefore had longer follow-up in the Medicare data.
- In addition, the relatively high frequency of bladder and other genitourinary cancers found in Medicare data suggests the theoretical possibility that local spread of advanced prostate cancer may in some instances have been recorded as SPM. In other words, some SPM found in the Medicare data may be false positives.
- We found one previous study of SPM in men with prostate cancer using SEER-Medicare data[11] that evaluated only colorectal cancer. Using only SEER outcome data, the incidence was 6.3 per 1,000 person-years (95% CI, 5.3-7.5) in men who had orchiectomies and 4.4 per 1,000 person-years (95% CI, 4.0-4.9) in those who were treated with gonadotropin-releasing hormone (GnRH) agonists. These investigators also conducted a sensitivity analysis using Medicare-documented cases and alluded to a discrepancy with their main analysis, but specific results were not reported. The crude incidence rate of CRC in our study was 7.2 per 1,000 person-years, but we used both SEER and Medicare data to identify SPM and our population was restricted to men with CRPC.
- Most SPM in our study were identified only in Medicare data. Given these findings, investigators should be aware that SEER-Medicare data may yield varying estimates of SPM depending on case identification criteria. Lower incidence rates are likely to be estimated using SEER-registered diagnoses of SPM than using both SEER and Medicare data files. Sensitivity analyses can be useful to understand the extent of differences in case identification with varying criteria.

Table 7. Types of Second Primary Malignancies Found Using SEER and Medicare

Cancer Type	n	%
Lung/bronchus	29	16.9
Urinary bladder	22	12.8
Colon/rectum	21	12.2
Non-prostate, non-bladder genitourinary tract	18	10.5
Non-colorectal gastrointestinal	17	9.9
Non-Hodgkin lymphoma and myeloma	15	8.7
Brain	14	8.1
Miscellaneous or unspecified	13	7.6
Meninges, head, neck, and endocrine	12	7.0
Melanoma, breast, and nipple	11	6.4
Total	**172**	**100.0**

Non-colorectal gastrointestinal = cancers of the esophagus, stomach, small intestine, liver, biliary tract, and pancreas.
Non-prostate, non-bladder genitourinary tract = cancers of the kidney, ureters, urethra, and testis.

DISCLOSURES

C. Saltus, D. Harris, B. Calingaert, J. Kaye, and E. Andrews are employees of RTI Health Solutions, which received funding from Bayer HealthCare Pharmaceuticals, Inc. to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. RTI conducts work for government, public, and private organizations, including pharmaceutical companies. J. Zong, G. Brobert, and M. Soriano-Gabarro are employees of Bayer.

This study was conducted using data from NCI's SEER program of the United States and guided by a data use agreement between NCI and RTI Health Solutions.

REFERENCES

Please see handout for a complete list of references.

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