

Catherine B Johannes,¹ Elizabeth B Andrews,² Lisa J McQuay,² Mark W Frohlich,³ Robert B Sims³

¹RTI Health Solutions, Waltham MA, United States; ²RTI Health Solutions, Research Triangle Park, NC, United States; ³Dendreon Corporation, Seattle, WA, United States

BACKGROUND

- Cerebrovascular accident (CVA) is a known complication of malignancy, but its incidence in men with prostate cancer is unknown.
- Prostate cancer is a commonly occurring cancer with a high 5-year relative survival rate and low ratio of deaths to new cases.¹ Thus men with prostate cancer may live for a prolonged period of time and be at greater risk for developing other medical conditions than cancer patients with a shorter life expectancy.
- CVA has been documented following clinical trials of patients with advanced hormone-refractory prostate cancer, and safety warnings about increased risk of stroke and other cardiovascular diseases in advanced prostate cancer patients were recently added to labels of gonadotropin-releasing hormone agonists.
- Published data on the incidence of CVAs in a general population of men with various stages of prostate cancer are lacking.

OBJECTIVE

- To estimate the incidence of new onset CVAs after diagnosis of prostate cancer among male, United States, Medicare enrollees aged 65 years and older and in similarly aged men without prostate cancer.

METHODS

Retrospective cohort study

Data Sources

Prostate Cancer Cohort

- Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database
 - Population-based, represents about 14% of United States population
 - 13 SEER cancer registries, collect data on incident cancers and vital status
 - Linkage with Medicare data, successful for 93% of persons aged 65 years and older

Nonprostate Cancer Comparison Cohort

- Medicare summarized denominator file
 - 5% sample of Medicare beneficiaries residing in SEER areas without reported cancer
 - Persons in SEER-Medicare linked file with cancer other than prostate cancer

Study Populations

Prostate Cancer Cohort

- Initial diagnosis of prostate cancer (stage I-IV) between January 1, 1999, and December 31, 2005
- Linked Medicare data from January 1, 1991, through December 31, 2007
- Enrolled in Medicare Parts A and B, not enrolled in health maintenance organization (HMO)
- Not originally entitled to Medicare benefits due to disability or end stage renal disease
- Aged 65 years or older at first prostate cancer diagnosis
- Did not have a date of death in the same month and year as initial diagnosis of prostate cancer
- Index date: date (month and year) of first prostate cancer diagnosis
- Baseline period: 12 months before index date

Nonprostate Cancer Comparison Cohort

- Same Medicare eligibility requirements as prostate cancer cases
- Selected according to index date of men in prostate cancer cohort
- Up to four controls randomly selected for each prostate cancer case according to case index date, matched on age of case at index date
- Study outcome: cerebrovascular event (CVA)

Hospital Case Definition (Ascertained in Both Cohorts)

- At least one ICD-9-CM diagnosis code on Medicare claim for inpatient hospitalization occurring as the primary hospital discharge diagnosis
 - Ischemic event: 433.x1, 434.x1, or 436
 - Hemorrhagic event: 430.xx, 431.xx, or 432.9
- First claim occurring after index date
- Excluded transient ischemic attacks (TIAs)
- Based on validated algorithm²
- Excluded men with claims evidence of CVA or TIA in baseline period

Death From CVA (Ascertained Only in Prostate Cancer Cohort)

- Evaluated from cause of death codes for CVA in last follow-up available from SEER vital status data
 - Death occurred after diagnosis of prostate cancer
- Variables**
- Age, race
 - Stage of prostate cancer at diagnosis (from SEER information)
 - Weighted comorbidity index based on the Klabunde and colleagues³ adaptation of the Charlson Comorbidity Index,⁴ modified to exclude cerebrovascular disease
 - Calculated from diagnosis codes in the Medicare claims in the year before the index date (baseline period)
 - Dichotomized into low (0-1) and high (≥ 2)

Analysis

Incidence rates: number of men with an incident CVA divided by amount of person-time

- Person-time in years: time from index date to earliest date of first CVA event, date of death, date of loss to follow-up (no longer covered by Medicare Parts A and B, HMO coverage initiated), or study ending date (December 31, 2007)
- Incidence rates (IR): number of men with CVA per 1,000 person-years, 95% confidence intervals (CIs)
 - Prostate cancer and comparison cohorts:** Incidence rates for hospital events only
 - Stratified by 5-year age groups, race, and comorbidity score at baseline
 - Prostate cancer cohort only:** Incidence rates for hospital events and deaths from CVA (not associated with a hospitalization)
 - Stratified by 5-year age groups, race, comorbidity score, stage of prostate cancer at diagnosis, age group within stage, and castration status in follow-up for the subgroup of men with advanced prostate cancer
- Incidence rate ratio (IRR) to compare CVA hospital events in the prostate cancer cohort to the comparison cohort computed by Poisson regression, adjusted for race, region, and comorbidity score

RESULTS

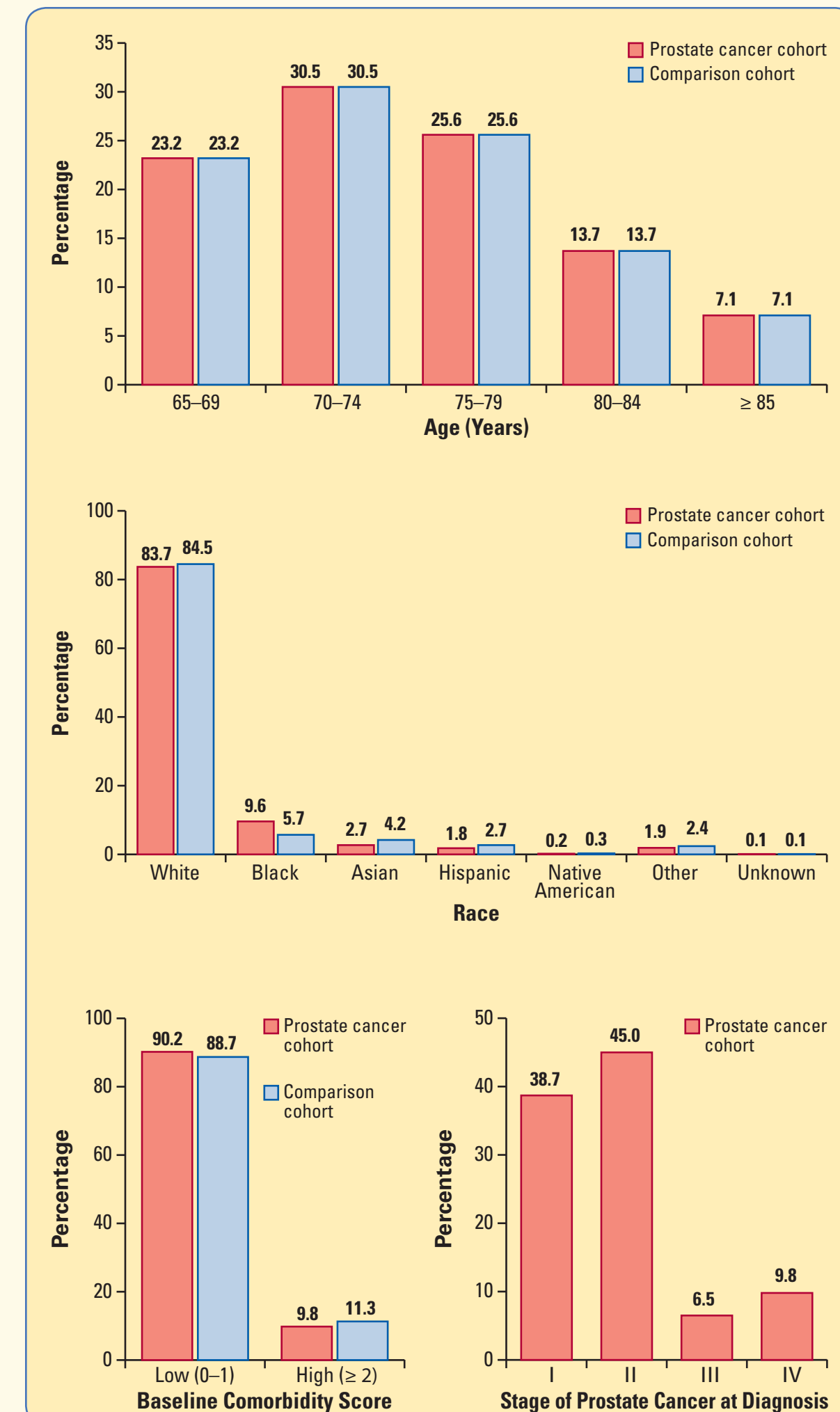
- Initial SEER-Medicare data file: n = 283,913 men with prostate cancer; final study cohort: N = 77,110

Table 1. Study Participants

| Reason for Exclusion | Number of Men Excluded |
|--|------------------------|
| Ineligible Medicare coverage and/or Medicare entitlement reason other than age | 165,567 |
| Aged < 65 years at diagnosis or age unknown | 97 |
| Missing information on prostate cancer stage or stage 0 | 38,966 |
| Claims for CVA or TIA in baseline | 1,829 |
| Prostate cancer diagnosis in same month as date of death | 344 |

- Four comparison subjects matched to each prostate cancer case on age and index date (N = 308,440)

Figure 1. Characteristics of Men With Prostate Cancer in Study Cohort, SEER-Medicare Database (January 1, 1999-December 31, 2007) (N = 77,110) and Nonprostate Cancer Comparison Cohort (N = 308,440)



N/A = not applicable.

Table 2. Incidence of CVA (Hospital Events Only)^a in Men with Prostate Cancer and in Nonprostate Cancer Comparison Cohort, and Stratified by Age and Baseline Comorbidities

| Stratification Category | Prostate Cancer Cohort | | | Nonprostate Cancer Comparison Cohort ^b | | |
|------------------------------------|------------------------|--------------|--------------------------|---|--------------|--------------------------|
| | n Events | Person-Years | IR ^c (95% CI) | n Events | Person-Years | IR ^c (95% CI) |
| Overall incidence | 2,697 | 310,236 | 8.7 (8.4-9.0) | 11,648 | 1,280,829 | 9.1 (8.9-9.3) |
| Age, years | | | | | | |
| 65-69 | 336 | 76,333 | 4.4 (3.9-4.9) | 1,476 | 311,978 | 4.7 (4.5-5.0) |
| 70-74 | 709 | 101,203 | 7.0 (6.5-7.5) | 2,991 | 414,196 | 7.2 (7.0-7.5) |
| 75-79 | 819 | 80,590 | 10.2 (9.5-10.9) | 3,517 | 330,539 | 10.6 (10.3-11.0) |
| 80-84 | 516 | 37,252 | 13.9 (12.7-15.1) | 2,302 | 157,169 | 14.6 (14.1-15.3) |
| 85+ | 317 | 14,859 | 21.3 (19.0-23.8) | 1,362 | 66,947 | 20.3 (19.3-21.5) |
| Baseline comorbidity score | | | | | | |
| Low (0-1) | 2,294 | 286,020 | 8.0 (7.7-8.4) | 9,766 | 1,166,279 | 8.4 (8.2-8.5) |
| High (≥ 2) | 403 | 24,217 | 16.6 (15.1-18.3) | 1,882 | 114,550 | 16.4 (15.7-17.2) |
| Prostate cancer stage | | | | | | |
| I-III | 2,443 | 289,099 | 8.5 (8.1-8.8) | N/A | N/A | N/A |
| IV | 254 | 21,137 | 12.0 (10.6-13.6) | N/A | N/A | N/A |
| On castration therapy ^c | 314 | 9,857 | 15.1 (13.5-16.9) | N/A | N/A | N/A |

IR = incidence rate per 1,000 person-years.

^a Information on deaths was not available for the nonprostate cancer comparison group.

^b Comparison subjects were matched to prostate cancer cases on age at index date (date of prostate cancer diagnosis).

^c Surgical castration or hormone therapy; analyses were performed in the subgroup of prostate cancer patients (n = 14,054) with advanced metastatic prostate cancer at baseline or with claims evidence of metastatic disease in Medicare follow-up claims.

Table 3. Incidence of CVA (Hospitalization for CVA or Death From CVA) in Men With Stages I-IV Prostate Cancer, by Age Group at Cancer Diagnosis, Stage at Diagnosis, Comorbidity Score at Baseline, and Age Group by Stage, SEER-Medicare Data

| Stratification Category | n Events | Person-Years | IR (95% CI) ^a |
|--|----------|--------------|--------------------------|
| Overall | 2,951 | 310,236 | 9.5 (9.2-9.9) |
| Age, years | | | |
| 65-69 | 351 | 76,333 | 4.6 (4.1-5.1) |
| 70-74 | 741 | 101,203 | 7.3 (6.8-7.9) |
| 75-79 | 903 | 80,590 | 11.2 (10.5-12.0) |
| 80-84 | 578 | 37,252 | 15.5 (14.3-16.8) |
| 85+ | 378 | 14,859 | 25.4 (22.9-28.1) |
| Stage of prostate cancer at diagnosis | | | |
| I-III | 2,660 | 289,099 | 9.2 (8.9-9.6) |
| IV | 291 | 21,137 | 13.8 (12.2-15.4) |
| Baseline comorbidity score | | | |
| Low (0-1) | 2,497 | 286,020 | 8.7 (8.4-9.1) |
| High (≥ 2) | 454 | 24,217 | 18.7 (17.1-20.6) |
| Stages I-III | | | |
| Comorbidity score | | | |
| Low (0-1) | 2,255 | 266,625 | 8.5 (8.1-8.8) |
| High (≥ 2) | 405 | 22,475 | 18.0 (16.3-19.9) |
| Stage IV | | | |
| Comorbidity score | | | |
| Low (0-1) | 242 | 19,395 | 12.5 (11.0-14.2) |
| High (≥ 2) | 49 | 1,742 | 28.1 (20.8-37.2) |
| Stages I-III | | | |
| Age, years | | | |
| 65-69 | 312 | 70,739.6 | 4.4 (3.9-4.9) |
| 70-74 | 677 | 95,125.7 | 7.1 (6.6-7.7) |
| 75-79 | 832 | 76,023.8 | 10.9 (10.2-11.7) |
| 80-84 | 524 | 34,354.9 | 15.3 (14.0-16.6) |
| 85+ | 315 | 12,855.3 | 24.5 (21.9-27.4) |
| Stage IV | | | |
| Age, years | | | |
| 65-69 | 39 | 5,593.2 | 7.0 (5.0-9.5) |
| 70-74 | 64 | 6,076.8 | 10.5 (8.1-13.4) |
| 75-79 | 71 | 4,566.5 | 15.5 (12.1-19.6) |
| 80-84 | 54 | 2,896.7 | 18.6 (14.0-24.3) |
| 85+ | 63 | 2,003.8 | 31.4 (24.2-40.2) |

^a Incidence rate per 1,000 person-years.

Results Summary

- Overall the incidence of CVA was similar in men with prostate cancer and in similarly aged men without prostate cancer. The IRR comparing the prostate cancer cohort with the comparison cohort adjusted for race and geographic region, and comorbidity score was 0.95 with a 95% CI of 0.91 to 0.99.
- In both cohorts, the risk of CVA increased with increased age at baseline and was higher for men with a high baseline comorbidity score.
- Among men with prostate cancer, the risk of CVA was higher in men with advanced stage disease and in those on castration therapy.

CONCLUSIONS

- CVA is an important cause of morbidity and mortality in men with prostate cancer, which has a relatively good prognosis compared with most other malignancies.
- Advanced prostate cancer patients have an increased risk of CVA compared with prostate cancer patients with nonadvanced disease and with similarly aged men without diagnosed prostate cancer.
- These data can inform baseline rates for understanding events occurring following introduction of new prostate cancer treatments.

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CONFLICT OF INTEREST

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CONTACT INFORMATION

Catherine Johannes, PhD

Director, Epidemiology

RTI Health Solutions
1440 Main Street, Suite 310
Waltham, MA 02451

Phone: +1.781.434.1784

Fax: +1.781.434.1701

E-mail: cjohannes@rti.org

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