The Impact of Prostate Specific Antigen Testing Frequency on Prostate Cancer Incidence and Treatment in Older Men

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Abstract

To quantify the downstream impact of prostate specific antigen (PSA) testing on cancer characteristics and utilization of cancer therapies among men aged 70 or older, we utilized patients diagnosed with prostate cancer in 2004–2005 in the Surveillance, Epidemiology, and End Results (SEER)-Medicare and their Medicare claims prior to their cancer diagnosis during 2000 to 2005.

Among men in the highest testing group (4–6 PSA tests), 75% were diagnosed with low- or intermediate- risk of disease but 77% received treatments within 180 days of cancer diagnosis. More than 45% of newly diagnosed patients in 2004–2005 had 4–6 PSA tests prior to their cancer diagnosis during 2000 to 2005. Men in the high testing group were 3.57 times more likely to receive cancer treatments (either surgery, radiation or hormonal therapy) when compared to men who had no prior PSA testing during the same time period. Among men aged 75+ diagnosed with low-risk cancer, men in the high testing group were 78% more likely to receive treatment than those who had no prior PSA testing.

In conclusion, given the lack of evidence of effective treatment for elderly patients diagnosed with low- and intermediate-risk prostate cancer and our inability to distinguish indolent from aggressive cancer, more frequent PSA testing among elderly population may exacerbate the risk of overdiagnosis and overtreatment.

Keywords

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Introduction

Screening for prostate cancer by prostate specific antigen (PSA) gained widespread acceptance in the United States following a 1987 report by Stamey et al.[1] More intensive PSA screening for prostate cancer has resulted in a higher prostate cancer incidence.[2] Unfortunately, no therapies have been shown to extend cause-specific survival for men over aged 65 diagnosed with low- or intermediate- risk prostate cancer.[3–5] Currently, the 5-year relative survival rate for patients diagnosed with localized disease is almost 100% regardless of whether patients receive therapy or not.[6] While PSA testing can detect prostate cancer at an earlier stage and potentially improve survival, it is also associated with a significant risk of overdiagnosis and overtreatment.[7]

The U.S. Preventive Services Task Force (USPSTF) recommends against PSA screening for men over age 75 due to the concern that the risk of overdiagnosis and overtreatment may outweigh the benefits of testing.[8] Despite evidence suggesting that PSA testing might be safely discontinued for most men older than 75,[9] the screening rate remains high in this group.[10,11] Since 2000 Medicare has paid for annual PSA testing without an upper age limit, eligibility requirements or evaluation. To quantify the downstream impact of PSA testing on utilization of treatments, we performed a nation-wide population-based study among Medicare recipients in the U.S.

Methods

Data Sources

We conducted a population-based retrospective cohort study utilizing data obtained from files linking information from the Surveillance, Epidemiology and End Results (SEER) program with Medicare claim files. The SEER regions encompass approximately 25% of the U.S. population, while the Medicare claim files cover approximately 93% of patients aged 65 years and older.[12] Age-specific population projections for 2010 to 2020 were obtained from the U.S. census.[13]

Study Participants

Our study included 24,356 prostate cancer patients diagnosed in 2004 and 2005 in the SEER-Medicare data who were continuously enrolled both Parts A and B as their primary health insurance since 2000. Men with missing PSA values, Gleason scores or clinical stage that prevented classification by risk strata were also excluded (n=2,349). A total of 22,047 men with prostate cancer were included in the final analysis. This study was approved by the institutional review board of the University of Medicine and Dentistry of New Jersey.

Measurement of PSA Testing and Treatment Intensity

We used claims for PSA testing from Current Procedure Terminology (CPT) codes 84153 or G0103 reported in the physician/supplier and outpatient files within Medicare as measurement of PSA testing intensity.[10,14] We calculated the number of claims for PSA testing from 2000 to 2005, excluding PSA testing that occurred after diagnosis of prostate cancer. More than 90% of men had only one claim for PSA testing each year. We counted multiple PSA test men received in one-year period as one single PSA test because we would like to estimate the proportion of men receiving at least one PSA testing before cancer diagnosis. The study population was divided into five groups (never, one, two, three, or four to six tests) based on the number of annual PSA tests received from 2000 to 2005.

Treatment administered following diagnosis was categorized as either active treatment or conservative management. Active therapy consisted of men receiving radical prostatectomy,

radiation therapy (i.e., external beam radiation therapy and/or brachytherapy) or primary androgen deprivation therapy (PADT) within 180 days following diagnosis. Conservative management included men not receiving radical prostatectomy, radiation or PADT as recorded in the SEER-Medicare dataset.

Data Elements and Study Groupings

Patient characteristics and cancer status were measured at the time of cancer diagnosis. The health status of the study population was assessed using the Charlson co-morbidity Index,[15] a summary measure based on 19 chronic diseases selected and weighted according to their association with mortality. To study the association between health status and the chance to receive PSA testing, each study participant was assigned a Charlson score based on information available from Medicare physician, inpatient, and outpatient claims during the twelve month period prior to the start of 2000. [16] Based on this information, the study population was divided into three categories: good health (Charlson score 0); average health (Charlson score 1); and poor health (Charlson score 2). Other variables known to influence PSA testing including education level, income, race, geographic location, number of physician visits, and marital status were obtained from SEER-Medicare linkages to the 2000 U.S. census data.

To assess cancer status at diagnosis, men were categorized into three risk groups using the American Joint Committee on Cancer classification system,[17,18] PSA level and Gleason score: 1) low risk (stage T2a, PSA 10 ng/ml, Gleason score 6), 2) intermediate risk (stage T2b and T2c or PSA 10 to 20 ng/ml or Gleason score 7) or 3) high risk (stage T3 or T4 or PSA > 20 ng/ml or Gleason 8).

Data Analyses

The association between Gleason score, cancer stage, risk categories at diagnosis and the number of annual PSA tests received were evaluated by the Mantel-Haenszel statistic.[19] The association between age and PSA level at diagnosis and the number of annual PSA tests received was examined by one-way analysis of variance using linear contrast. The distribution of the number of annual PSA tests received prior to diagnosis stratified by age, race, health conditions, and other characteristics present at diagnosis was evaluated by the asymptotic Kruskal-Wallis test.[20]

We used ordinal logistic regression models to estimate multivariate-adjusted odds ratios and 95% confidence intervals to determine the association between each patient characteristic and the number of annual PSA tests received prior to diagnosis. In addition, we used multivariable logistic regression to estimate the association between each variable, the number of PSA tests received, and the receipt of treatments. The distribution of treatments stratified by the number of PSA tests and risk groups was evaluated using the Cochran-Mantel–Haenszel statistic.

All statistical tests were two-sided and were performed by using SAS version 9.1.3 (SAS Institute, Cary, NC).

Role of the Funding Source

RESULTS

Characteristics of the patients and their pre-diagnosis PSA testing use are described in Table 1. More than 45% (10017/22047) of newly diagnosed cancer patients in 2004 and 2005 had 4–6 PSA tests during 2000 and 2005 prior to their cancer diagnosis. Men who are white, with higher education, more affluent, married and had more physician visits one year prior to cancer diagnosis are more likely to receive a higher number of PSA tests before cancer diagnosis. Increasing numbers of PSA tests prior to cancer diagnosis were associated with decreasing PSA levels at diagnosis, lower biopsy Gleason scores, lower clinical stages and lower risk disease (p<.001) (Table 2). The median PSA at diagnosis decreased from 11.9 ng/ml for patients who had never been previously tested to 7.2 ng/ml for patients who received four to six annual tests (p<.001). Among men in the highest testing group (4 to 6 PSA tests), 75% were diagnosed with low- or intermediate- risk of disease but 77% received treatments in 180 days.

Factors predicting the frequency of annual PSA testing prior to diagnosis are listed in Table 3. In our initial model (results not shown), age was the strongest predictor of annual testing, but surprisingly, increased Charlson score was associated with an increased frequency of annual PSA testing after adjusting for other factors. We anticipated that number of physician visits might relate to the number of PSA tests received and included this variable in our final model. In this final model, the number of physician visits in one year before cancer diagnosis was strongly associated with the chance of receiving a PSA test (Table 3). Men in poor health status was no longer related to a higher chance of receiving PSA tests after adjusting for number of physician visits when compared with men in good health status. Patients who were white, married, or had relatively higher incomes and education had a higher chance to have annual PSA tests.

Factors predicting a higher frequency of PSA testing also predicted the likelihood of receiving cancer therapy (Table 3). Compared to men who had never been tested, the chance of receiving a cancer treatment was 2.83 (95% CI: 2.48–3.24) times in men who received only one PSA test and 3.57(95% CI: 3.14–4.05) times in men who received 4 to 6 PSA tests. This was true for men in all age categories and health conditions. Men who lived in the northeast area were more likely to receive treatments than men who lived in other regions.

Figure 1 presents the treatment pattern among men aged 75 and older who were diagnosed with prostate cancer stratified by the number of prior annual PSA tests and cancer risk groups. Men who received more than one PSA testing prior to diagnosis were more likely to receive treatments within 180 days (p<.005). In the low-risk group, men who underwent four to six PSA tests were 1.78 times more likely to received treatments compared with men who had not had annual PSA tests (p<.005). Radical prostatectomy and radiation therapy were more common among low- and intermediate risk patients than among high-risk patients.

DISCUSSION

Our findings suggest that men receiving more PSA tests before cancer diagnosis is associated with a higher chance in receiving cancer therapy. Among men in the highest testing group (4 to 6 PSA tests), 75% were diagnosed with low- or intermediate- risk of cancer but 77% received treatments in 180 days. Only 50% of men who had no prior PSA test received active therapy. Our previous study[7] showed that aggressive local therapy was provided to most patients diagnosed with prostate cancer due to the inability to distinguish indolent from aggressive cancers. Results from this study further demonstrated that more

intensive PSA testing among the elder population is likely to exacerbate the risk of overdiagnosis and overtreatment.

Screening in the U.S. is predominantly opportunistic. Opportunistic screening depends on the health care providers to recommend screening or on individuals to request screening. It involves fewer formal decisions regarding whom to screen, whether to screen and at what interval. Among men diagnosed with prostate cancer in 2004–2005, almost half have undergone annual PSA testing prior to their diagnosis and many of these men have a limited life expectancy. Our results demonstrate that PSA testing appears to correlate more with the number of physician visits rather than the risk of developing prostate cancer or the health status of the patient. The possibility that opportunistic screening could cause more harm than good has been a concern. [21] Although intensive PSA testing may diagnose patients at an earlier stage of cancer, data from ERSPC study demonstrated that cancers diagnosed from repeated screening has a minimal effect on detecting clinically significant disease, [22,23] and are not associated with reduced prostate cancer mortality.[2] Despite this evidence many clinicians continue to screen Medicare eligible men annually, possibly because they over estimate the benefit and do not appreciate the potential harms of PSA screening. Many may lack the time to explain the pros and cons of PSA screening strategies while others may be concerned about medical-legal implications. [24,25]

Our results support the USPSTF concern of screening men with less than a 10-year life expectancy because of the increased likelihood of harm from the consequence of screening relative to any potential benefit.[26] For men aged 75 and older with low-risk prostate cancer, active surveillance may be the best treatment option when compared to the treatment-related side effects and the modest survival benefit associated with more aggressive treatment. [3–5,27] However, we found that men with low-risk cancer were treated intensively after cancer diagnosis. Men who had 4 to 6 PSA tests prior to diagnosis were much more likely to receive treatment within 180 days, particularly radiation therapy, than men who did not have PSA test. Men who had assumed they would benefit from early detection and cancer treatment before receiving a PSA test and the number of PSA tests they received prior to cancer diagnosis could be interpreted as their level of belief regarding PSA screening for prostate cancer.

Medicare started to cover annual PSA tests since 2000 despite the uncertainty surrounding the cost-effectiveness to provide PSA testing for early detection.[28] In 2004, Medicare expenditures for prostate cancer ranked third highest among cancer patients after lung cancer and colorectal cancer.[29] Alone with evidence suggesting the lack of benefit to screen men who are aged 75 and above,[5] our data show that more frequent PSA testing and the subsequent diagnosis of additional prostate cancers often lead to more cancer therapies that may not result in reduced prostate cancer mortality. Therefore, specifying screening eligibility criteria and screening interval may yield benefits at the population level.[30,31] If Medicare beneficiaries follow the USPSTF recommendation of no screening after age of 75 or screened only once in a four-year interval, many men would be spared a cancer diagnosis and treatment. Consequently, Medicare costs would decrease dramatically with a modest impact on prostate cancer mortality.

Strengths and Limitations

This is the first population based study documenting the association between PSA testing frequency and prostate cancer treatment patterns among Medicare beneficiaries. The linked dataset provided the power to study the consequence of PSA testing because of its size but limited our analysis to men diagnosed with prostate cancer at age 70 years and older. We cannot distinguish PSA screening from diagnostic PSA testing in Medicare claims where men might receive PSA test because of symptoms. However, more than 40% of men in our

study diagnosed at T1c stage indicate that they were diagnosed from screening. Most of these men diagnosed at T1c stage were low- or intermediate- risk which did not need any intensive treatment necessarily, but they were mostly treated. Our analysis was unable to identify PSA testing that occurred outside of the Medicare reimbursement system. As a consequence, the prevalence of PSA testing may be even higher than recorded in our study. Furthermore, whether patients selected treatment because of their concerns about disease progression or were urged to undergo treatment by their treating physicians cannot be determined by this study.

The USPSTF recommendation against screening for men aged 75 and older is because of concerns that the risks may outweigh benefits among men with limited life expectancy. Our study supports the concerns by showing the substantial downstream effect on treatment utilization. Because prostate cancer progresses slowly and the ten year disease specific mortality is low,[32] we could not evaluate the association between PSA testing and prostate cancer specific mortality. Previous studies suggest that more intensive screening and treatment is not associated with lower prostate cancer mortality among elderly men.[2]

Conclusion

Our study reveals the profound impact of intensive PSA testing on cancer diagnosis and treatment. Given the lack of evidence of effective treatment for men older than 65 years of age diagnosed with low- and intermediate-risk prostate cancer and our inability to distinguish indolent from aggressive cancer, intensive PSA testing is likely to exacerbate the risk of overdiagnosis and overtreatment among elderly men.

Acknowledgments

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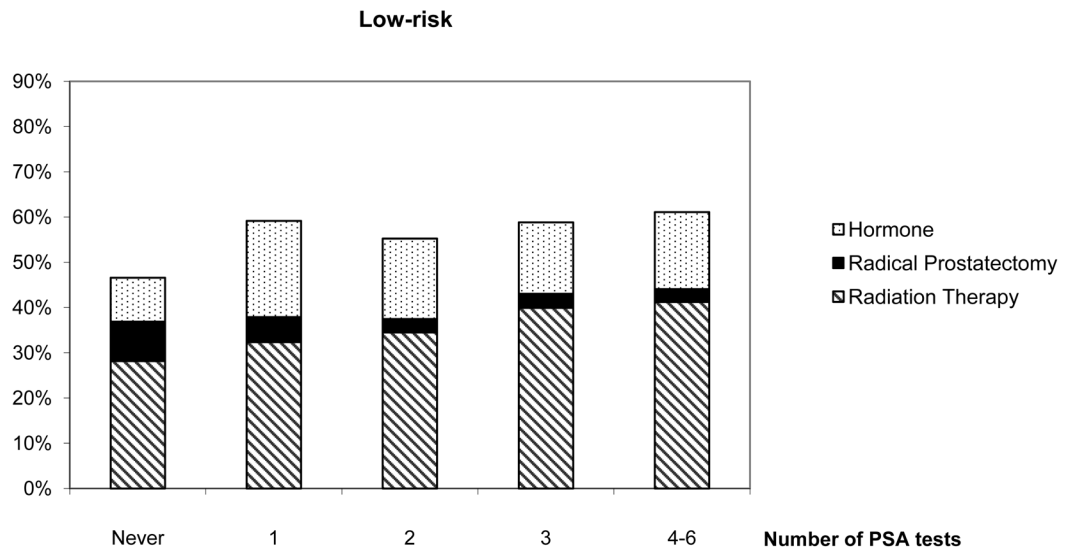
Fig 1A

Low-risk

Fig 1B

Intermediate-risk
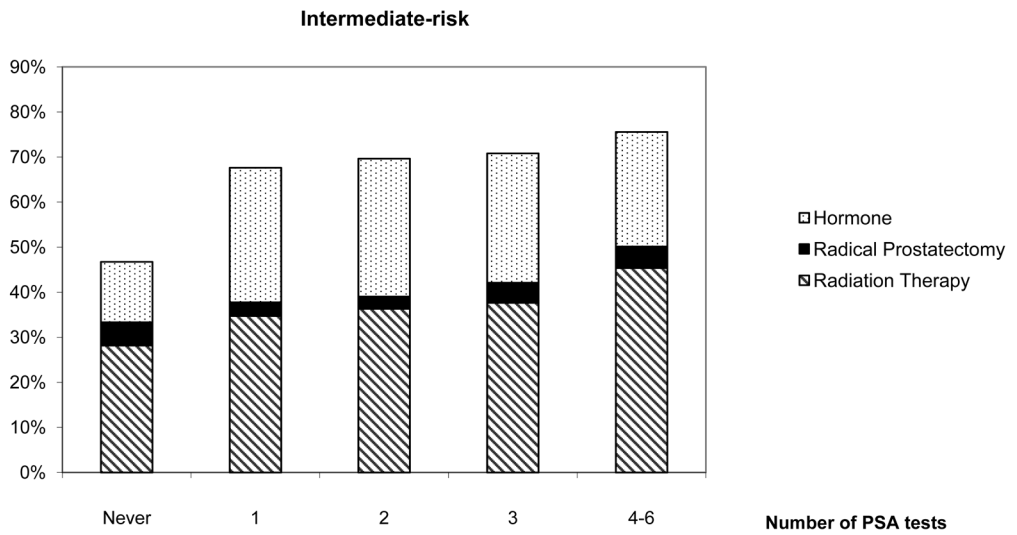
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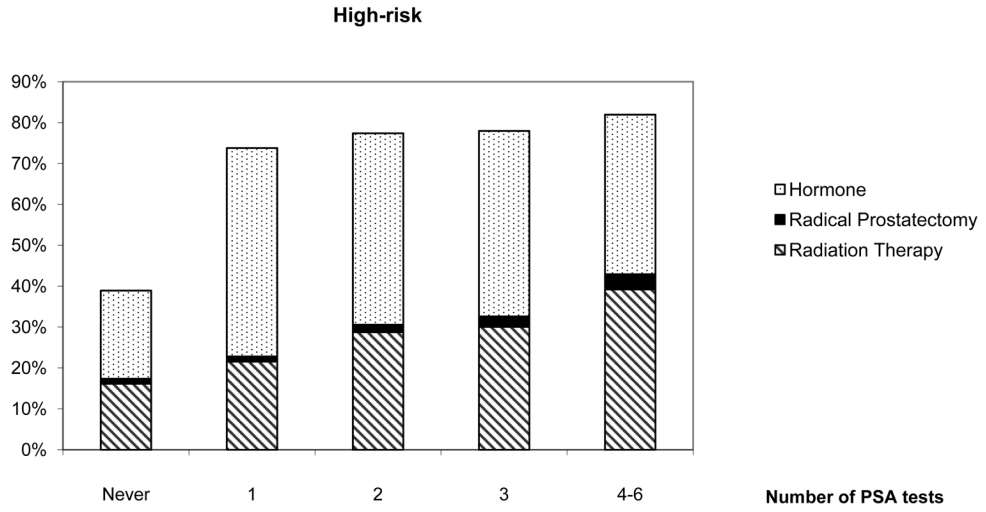
High-risk

Figure 1.
Treatment patterns among men aged 75 and older diagnosed with low-, intermediate- and high-risk prostate cancer by the number of prostate specific antigen (PSA) tests, SEER-Medicare 2004–2005.

Only radical prostatectomy, radiation therapy or hormone therapy received within 180 days after diagnosis were included.

* Radical prostatectomy includes patients who received radical prostatectomy alone or with radiation therapy or hormone within 180 days after diagnosis. Radiation therapy includes patients who received radiation therapy alone or with hormone.

+ Difference across number of PSA tests was statistically significant for all risk groups.

Table 1

Characteristics of men with prostate cancer by number of PSA testing received from 2000 to 2005 prior to diagnosis; SEER-Medicare database. (n=22,047)

Characteristics	Number of PSA screening test from 2000 to 2005 [*], n (%)				
	Never (n = 1446)	1 (n = 3692)	2 (n = 3362)	3 (n = 3530)	4 to 6 (n = 10017)
Age, y					
Mean age (SD)	77.4 (5.8)	77.3 (5.6)	76.8 (5.4)	76.6 (5.1)	76.7 (4.9)
Age, %					
70–74	569 (39)	1388 (38)	1406 (42)	1499 (42)	3934 (39)
75–79	413 (29)	1146 (31)	1007 (30)	1093 (31)	3422 (34)
80–84	272 (19)	706 (19)	606 (18)	637 (18)	1941 (19)
85+	192 (13)	452 (12)	343 (10)	301 (9)	720 (7)
Race, %					
White	1109 (77)	2915 (79)	2708 (81)	2956 (84)	8562 (86)
Black	241 (17)	462 (13)	351 (10)	284 (8)	614 (6)
Others	96 (7)	315 (9)	303 (9)	290 (8)	841 (8)
Region, %					
West	647 (45)	1582 (43)	1605 (48)	1717 (49)	4809 (48)
Northeast	295 (20)	759 (21)	676 (20)	707 (20)	2231 (22)
North Central	155 (11)	533 (14)	459 (14)	534 (15)	1528 (15)
South	349 (24)	818 (22)	622 (19)	572 (16)	1449 (14)
Lived in ZIP code tabulation area in which 25% or more of adults had a college education, %	503 (35)	1329 (36)	1360 (41)	1636 (46)	5347 (53)
Median annual income of ZIP code tabulation area, $	40,771	42,365	45,111	46,712	50,721
Marital Status, %					
Married	830 (57)	2198 (59)	2096 (62)	2335 (66)	6904 (69)
Health Status Based on Charlson Score, %					
0 (Good)	1251 (87)	3089 (84)	2706 (81)	2806 (80)	7964 (80)
1 (Average)	135 (9)	412 (11)	462 (14)	515 (15)	1552 (16)
>=2 (Poor)	60 (4)	191 (5)	194 (6)	209 (6)	501 (5)

Characteristics	Number of PSA screening test from 2000 to 2005 [*], n (%)					
	Never (n = 1446)	1 (n = 3692)	2 (n = 3362)	3 (n = 3530)	4 to 6 (n = 10017)
No. of physician visits one year before Cancer diagnosis [**]					
1st Quartile	972 (67)	1495 (40)	968 (29)	810 (23)	1590 (16)
2nd Quartile	190 (13)	898 (24)	867 (26)	930 (26)	2508 (25)
3rd Quartile	131 (9)	704 (19)	786 (23)	938 (27)	2938 (29)
4th Quartile	153 (11)	595 (16)	741 (22)	852 (24)	2981 (30)

[*]
Difference across number of PSA tests received prior to diagnosis were statistically significant (p<.001) for all characteristics.

[**]
Number of physician visits one year before cancer diagnosis was grouped by quartile: 1st: 0 to 7 times; 2nd: 8 to 13; 3rd: 14 to 23; 4th: 24 and above.

Table 2

Prognostic characteristics and treatments of men with prostate cancer by number of PSA testing received from 2000 to 2005 prior to diagnosis; SEER-Medicare database. (n=22,047)

Cancer Characteristics	Number of PSA screening tests from 2000 to 2005[*]				
	Never (n = 1446)	1 (n = 3692)	2 (n = 3362)	3 (n = 3530)	4 to 6 (n = 10017)
Median PSA (95% Confidence Interval), ug/mL	11.9	12.9	9.0	7.5	7.2
	(10.9, 13)	(12.3, 13.6)	(8.7, 9.3)	(7.2, 7.7)	(7.0, 7.3)
Gleason Score, %					
Gleason 2–4	16 (1)	31 (1)	36 (1)	33 (1)	98 (1)
Gleason 5–6	424 (29)	988 (27)	1166 (35)	1336 (38)	4358 (44)
Gleason 7	452 (31)	1329 (36)	1237 (37)	1295 (37)	3565 (36)
Gleason 8–10	371 (26)	1080 (30)	774 (23)	766 (22)	1772 (18)
Unknown	183 (13)	264 (7)	149 (4)	100 (3)	224 (2)
Stage, %					
T1	573 (40)	1384 (38)	1465 (44)	1571 (45)	4880 (49)
T2	626 (43)	1765 (48)	1581 (47)	1686 (48)	4599 (46)
T3/T4	110 (8)	266 (7)	165 (5)	141 (4)	252 (3)
Unknown	137 (9)	277 (8)	151 (4)	128 (4)	286 (3)
Risk group, %					
Low	279 (19)	617 (17)	801 (24)	1109 (29)	3171 (32)
Intermediate	496 (34)	1292 (35)	1362 (41)	1434 (41)	4325 (43)
High	671 (46)	1786 (48)	1199 (36)	1087 (31)	2521 (25)
Treatment in 180 days, %					
Conservative Management	716 (50)	954(26)	842 (25)	859 (24)	2282 (23)
Radical Prostatectomy	74 (5)	238 (6)	270 (8)	310 (9)	984 (10)
Radiation Therapy	457 (32)	1291 (35)	1352 (40)	1536 (44)	4742 (47)
Hormone Therapy	199 (14)	1209 (33)	898 (27)	825 (23)	2009 (20)

[*] Difference across number of PSA tests received prior to diagnosis were statistically significant (p<.001) for all characteristics.

Table 3

Multivariable model of characteristics associated with receiving PSA tests prior to diagnosis and with initial treatments in 180 days, SEER-Medicare database. (n=22,047)

	Outcome	
	For PSA tests[*]	**For Treatments**[**]
Characteristics	**Adjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio (95% CI)**
No. of PSA tests		
1 vs None	-	2.83 (2.48, 3.24)
2 vs None	-	3.07 (2.67, 3.52)
3 vs None	-	3.21 (2.79, 3.69)
4 vs None	-	3.57 (3.14, 4.05)
Age		
70–74 vs 85+	1.73 (1.58, 1.89)	3.52 (3.14, 3.94)
75–79 vs 85+	1.77 (1.62, 1.94)	2.23 (1.99, 2.49)
80–84 vs 85+	1.54 (1.40, 1.70)	1.38 (1.23, 1.54)
Race		
Black vs White	0.68 (0.63, 0.75)	0.79 (0.71, 0.89)
Others vs White	0.93 (0.85, 1.02)	0.78 (0.70, 0.87)
Region		
North Central vs West	1.23 (1.14, 1.33)	1.18 (1.07, 1.30)
Northeast vs West	0.93 (0.87, 1.00)	1.53 (1.40, 1.67)
South vs West	0.85 (0.79, 0.92)	1.13 (1.03, 1.24)
Lived in ZIP code tabulation area in which 25% or more of adults had a college education		
Yes vs No	1.40 (1.31, 1.49)	1.01 (0.93, 1.09)
Median annual income of ZIP code tabulation area[†]		
High vs Low	1.26 (1.16, 1.36)	1.07 (0.97, 1.19)
Mid vs Low	1.13 (1.05, 1.21)	1.06 (0.97, 1.16)
Marrital Status		
Yes vs no	1.27 (1.21, 1.34)	1.62 (1.52, 1.73)
Charlson score		
1 (Average) vs 0 (Good)	1.14 (1.06, 1.23)	0.97 (0.88, 1.06)
>=2 (Poor) vs 0 (Good)	0.84 (0.76, 0.95)	0.89 (0.78, 1.03)
No. of physician visits one year before Cancer diagnosis[‡]		
2nd Quartile vs 1st Quartile	2.70 (2.52, 2.89)	1.15 (1.05, 1.26)
3rd Quartile vs 1st Quartile	3.54 (3.30, 3.79)	1.13 (1.03, 1.25)
4th Quartile vs 1st Quartile	3.97 (3.69, 4.27)	1.10 (1.00, 1.20)
Risk Group		
Low vs High	-	0.34 (0.31, 0.37)
Intermediate vs High	-	0.72 (0.66, 0.78)

Treatments include radical prostatectomy, radiation therapy and primary androgen deprivation therapy.

*
Modeling the risk of receiving PSA tests adjusted for all variables in the table, except Number of PSA tests and Risk Group.

**
Modeling the risk of receiving treatments adjusted for all variables in the table.

†
Median annual income of ZIP code tabulation area was categorized into High: >=$50,000; Middle: >=35,000; <50,000, Low: <35,000.

‡
Number of physician visits one year before cancer diagnosis was grouped by quartiles: 1st: 0 to 7 times; 2nd: 7 to 13; 3rd: 13 to 23; 4th: 23 and above.