Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ 7/21/2014_____

Shuang Lin Date

Predictors of Patients with Clinically Insignificant Prostate Cancer to Harbor Significant Cancer

By

Shuang Lin
Degree to be awarded: MPH

Epidemiology

_____

Kevin C. Ward
Committee Chair

Predictors of Patients with Clinically Insignificant Prostate Cancer to Harbor Significant Cancer

By

Shuang Lin

MD
Southern Medical University
2012

Thesis Committee Chair: Kevin C. Ward, PhD, MPH, CTR

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2014

ABSTRACT

Predictors of Patients with Clinically Insignificant Prostate Cancer to Harbor Significant Cancer

By Shuang Lin

Introduction: The discrepancy of prostate cancer results between biopsy and prostatectomy is common. Our study aim was to identify factors that could help predict more advanced disease in patients with clinically insignificant prostate cancer.

Method: We identified 15,892 prostate cancer cases from the Surveillance, Epidemiology, and End Results (SEER) database diagnosed with clinically insignificant PCa between 2010 and 2011. Clinically insignificant prostate cancer was defined using the following criteria: locally confined prostate cancer based on clinical staging (clinical AJCC stage T1-T2) with a biopsy Gleason score of 3+3. Categorical variables were assessed using chi-square tests. Multivariate logistic regression modeling was used to assess predictors of more advanced disease following prostatectomy.

Results: Of the 15,489 patients eligible for the study, 8,010 patients (52%) experienced a shift from clinically insignificant PCa to significant PCa, including 1,228 patients (8%) shifting to AJCC stage T3-T4, 4,647 patients (30%) upgraded to GS>=7 (or any GS containing grade 4 or 5), and 2,135 (14%) patients experiencing both an upgraded GS and a shift in AJCC stage. Higher PSA and older age were the two strongest predictors. Race, SEER region and poverty were also independent predictors for selected groups.

Conclusions: Patients diagnosed with clinically insignificant prostate cancer may harbor significant cancer. Future work should look for ways to improve the accuracy of clinical measurements so that clinicians can minimize the probability of misclassification and more accurately classify patients prior to treatment so that more informed decision making can occur.

Key words: SEER, Biopsy, Prostatectomy, Prostate Cancer, Predictor, Insignificant, Significant

Predictors of Patients with Clinically Insignificant Prostate Cancer to Harbor Significant Cancer

By

Shuang Lin

MD
Southern Medical University
2012

Thesis Committee Chair: Kevin C. Ward, PhD, MPH, CTR

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2014

Table of Contents

BACKGROUND

The prostate is an accessory gland of the male reproductive system that is just under the bladder. It comes from epithelial budding of the urogenital sinus, which surrounds the urethra (1). The urethra forms the route for sperm release (1). The prostate gland contains three major zones: the central, transitional, and peripheral zones(2). The peripheral zone, which is the largest zone of the prostate, is the site that has the majority of prostate cancer (1, 3).

Prostate cancer (PCa) is now the most common malignancy among men in the United States, with an estimated 241,740 new cases and 28,170 deaths in 2012 (4). The exceptionally high incidence of prostate cancer is an area of controversy to many as concerns exist regarding over-diagnosis and over-treatment of this disease (5-7). Autopsy studies suggest that most aging men will develop lesions that would be diagnosed as prostate cancer (8). However, most of these patients' PCa are indolent cancers (8). Many patients died with the cancer instead of from the cancer. With any new cancer diagnosis, there is a tendency for the patient to seek treatment and the clinician to offer treatment. For PCa, common treatments include surgery (radical prostatectomy), radiation, cryosurgery, endocrine therapy or active surveillance (AS). While treatment is generally advisable for most cancers, any benefit from the treatment or screening policy should be weighed against the harms in terms of the possibilities of over-diagnosis and over-treatment associated with that policy (9). This is especially true for very early stage, indolent cancers where there exists the potential for a negative impact from early detection and subsequent treatment. Studies from the

American Cancer Society (ACS) showed that prostate cancer treatment can cause a series of adverse effects on patients, including urinary incontinence, anatomic stricture of the urinary tract, and sexual dysfunction (10-12), which can greatly affect patients' life quality. In order to minimize over-diagnosis and over-treatment, in 2010, the ACS updated its guideline for the early detection of prostate cancer as a result of these studies. The new guidelines recommended that asymptomatic men who have at least a 10-year life expectancy have an opportunity to make informed decision with their health care providers about screening for PCa after they are aware of uncertainties, potential risks, and benefits of screening (9). The guideline also mentioned that there is no current published evidence that is related to the quality of life impact of active surveillance with screen-detected cancers compared with unscreened men. Therefore, clinicians currently consider active surveillance as an alternative treatment for low risk, organ-confined PCa (13).

While active surveillance warrants consideration in the portfolio of optional treatments, studies have shown that it may lead to the under diagnosis of unfavorable pathologic findings (5, 13). This means that some patients diagnosed with asymptomatic prostate cancer may harbor more advanced disease than what was clinically identified. Several studies have reported that about 30% to 34% of aging men will have their Gleason score, which is a score for grading prostate tissue based on how it looks under the microscope and ranges from 2 to 10 (14), upgraded after radical prostatectomy (15-17). These patients may show evidence of more advanced pathologic extension or invasion (15), and some patients may even experience

progressions of their diseases (15). In order to address some of these issues and provide guidelines, clinicians and researchers have attempted to categorize PCa into clinically insignificant and significant.

Clinically insignificant cancer is defined as a cancer which is confined to the organ and is not expected to harm the patient during the natural course of his lifetime (18). Numerous attempts have been made to define clinically insignificant prostate cancer, most of which focused on tumor volume, surgical margin status, pathologic stage, and grade (18-20). In 1993, Stamey et al defined clinically insignificant PCa as organ-confined tumors of $<0.5cm^3$ with Gleason score 3+3 (18, 19). In 1998, D'Amico et al defined PCa with stage<=T2a, biopsy GS<=6, and PSA<=10ng/ml, as insignificant (21). This became known as the D'Amico criteria. After that, in 2011, Wolters et al redefined insignificant PC as organ-confined Gleason 3+3 tumors, the largest tumor having a volume$<=1.3cm^3$ and a total volume$<=2.5cm^3$ (18, 22).

Many studies have found that there were discrepancies between the initial biopsy result and the result of the prostatectomy. Hasmet et al discovered that of their 321 PCa patients diagnosed between 2007 and 2013 with an initial biopsy Gleason score<=6 who had all undergone prostatectomy afterwards, 131 (40.8%) of them had a prostatectomy GS that upgraded to 7 or higher (23). In order to identify factors that can predict such upgrade, they discovered that patients with small prostates (<=40cc), greater than 1 core positive for cancer, and a maximum percent of cancer in any core are associated with the upgrade of GS (23). However, this study only focused on the

predictors of upgrading Gleason score, but not on the whole criteria that can define significant and insignificant cancer. In 2012, Song et al, using the D'Amico criteria to define insignificant cancer, found that an anterior site of cancer on magnetic resonance imaging is useful in predicting GS upgrading and also unfavorable pathologic outcomes. This research greatly helped to clarify the effect of imaging on disease progression (5). Besides the two studies mentioned above, there are other studies that have been done in order to look for predictors of PCa upgrading. Seisen et al discovered that PSA>15ng/ml, age>70, number of biopsy cores>12, length of cancer per core>5 mm, and prostate weight>50 g are predictors of GS upgrading (24). In 2011, Milonas et al demonstrated that PSA density (PSAD) is another predictor of GS upgrading within a 5-year duration (2002-2007) (25). Most of these studies were conducted with hospital or clinic based samples of limited size. Our study aims were two-fold. The first aim was to provide informative descriptive clinical cancer characteristics of a population-based sample of United States men with prostate cancer. The second aim was to further identify within this cohort variables that could help predict which patients following pathologic assessment of their cancer were likely to harbor more advanced disease characteristics compared to the original clinical assessment.

METHODS

Data sources

Prostate cancer cases were selected from the Surveillance, Epidemiology, and End Results (SEER) database. The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States. SEER reports long-term, high-quality incidence, prevalence, and survival data. Long-term incidence and survival trends are based on the data from the 9 oldest SEER areas (Connecticut, Iowa, Hawaii, New Mexico, Utah, and the metropolitan areas of Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound), which represent about 10% of the US population (26). In 1992, SEER expanded to include another 4 populations (Alaska Natives, Los Angeles County, San Jose-Monterey, and rural Georgia) that increased coverage of minority groups (26). SEER expanded again in 2000 adding 5 additional catchment areas (greater California, greater Georgia, Kentucky, Louisiana, and New Jersey). With this most recent expansion, SEER coverage reached 28% of the overall US population (26). In 2010, SEER began for the first time to collect data on both biopsy and prostatectomy, where applicable, Gleason scores. These data in conjunction with the clinical and pathologic extension of disease, which have routinely been collected by SEER, form the basis for this research. The most current SEER dataset contains cases through diagnosis year 2011.

Study Cohort

Between diagnosis years 2010 to 2011, 112,475 male patients were diagnosed with

prostate cancer (adenomas/adenocarcinomas) in SEER data. Because tumor volume is not collected in SEER, clinically insignificant prostate cancer was defined using the following criteria: locally confined prostate cancer based on clinical staging (27) (clinical AJCC stage T1-T2) with a biopsy Gleason score of 3+3. 44,347 (39.4%) of the cohort defined above met this definition. In order to define the transition to significant PCa on pathologic examination, cases were required to have a prostatectomy so that we could evaluate both the Gleason score and AJCC stage from the resection. Additional exclusions due to missing data narrowed the final cohort to 15,489 patients (Figure 1).

Outcomes

The outcome of interest in this study was categorized into two groups based on pathologic results from the prostatectomy: the patient still had insignificant prostate cancer or the patient no longer had insignificant prostate cancer. Prostate cancer with a pathologic Gleason score of 6 (without grade 4 or 5) and pathologic stage T1-T2 was defined as “still insignificant”; prostate cancer with a pathologic Gleason score greater than 6 (or with any grade 4 or 5) or a pathologic AJCC stage greater than T2 was called “no longer insignificant”.

Variable Description

Variables involved in this study as potential predictors were race, age at diagnosis, prostate specific antigen (PSA) lab values, sequence number, SEER registry, marital status, insurance, poverty, and high school education. Race was categorized into 5

groups (white, black, Hispanic, others, unknown) and age at diagnosis was defined into 4 groups (0-54 yrs, 55-59 yrs, 60-64 yrs, 65+ yrs). PSA lab values were defined into 5 categories (0-5, 5-10, 10-20, 20+, unknown). In SEER data, the PSA value is the highest PSA lab value documented in the medical record prior to diagnostic biopsy of prostate and treatment. Sequence number, which is a count of the number of primary cancers of a patient, was defined into 2 groups (one or more primaries, one primary only); SEER registry was defined into 4 categories based on geographic locations: North (Connecticut, New Jersey), South (Atlanta, Rural Georgia, Kentucky, Louisiana, Greater Georgia), Midwest (Detroit, Iowa), and West (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles, Greater California, Alaska); marital status was divided into 2 groups (married, others); and insurance was defined into 4 groups (Private insurance, any Medicaid, uninsured, unknown). SEER does not collect data on individual level poverty or education. Instead, they create area-based measures of socioeconomic status using census tract information from the patient's address at the time of diagnosis in conjunction with census tract level SES characteristics from the United States Census Bureau. In this study, area-based poverty for each individual case was defined as the percentage of the census tract population in which the case resided with an income below the federal poverty level. Poverty was categorized into 4 groups (0-5%, 5%-10%, 10%-20%, 20%+). Area-based education for each case was defined as the percentage of the census tract population in which the case resided with less than high school education level and was categorized into 4 groups (10.5%, 10.5%-13.79%, 13.79%-20.15%, 20.15%).

Statistical Analysis

Analyses focused on predictors of patients with clinically insignificant prostate cancer to harbor significant cancer on pathologic examination. Categorical variables were evaluated using chi-square tests for univariate analyses. Multivariate predictive modeling with logistic regression was conducted to examine factors associated with the outcome of interest. We compared both full (all covariates) and reduced (significant covariates based on backward elimination) models for predictive assessment. Interaction was assessed between race and insurance, race and PSA lab value, and race and age. No significant interactions were identified. All statistical analyses were performed by using SAS software version 9.3 (SAS Institute, Inc., Cary, NC). A p value of 0.05 was considered statistically significant.

RESULTS

After restricting the cohort to cases with no clinical lymph node involvement or distant metastasis, Table 1 presents the distribution of biopsy Gleason scores by clinical extension. 45,487 (40.4%) patients had locally confined prostate cancer (T stage of T1-T2) with a GS of 6. Furthermore, 44,347 (39.4%) patients met the study definition of clinically insignificant PCa, having a 3+3 Gleason pattern and a clinical stage of T1-T2. This 3+3 pattern represented the largest proportion of patients compared to the other Gleason patterns (Table 1).

Of the 15,489 patients eligible for the study (Figure 1), 7,479 (48%) patients remained in the category of clinically insignificant PCa following pathologic assessment of the prostatectomy specimen. 8,010 patients (52%) experienced a shift from clinically insignificant PCa to significant PCa, including 1,228 patients (8%) shifting to AJCC stage T3-T4, 4,647 patients (30%) upgraded to GS>=7 (or any GS containing grade 4 or 5), and 2,135 (14%) patients experiencing both an upgraded GS and a shift in AJCC stage.

In univariate analyses, statistically significant differences in the outcome groups (insignificant vs. significant cancer) were observed for race ($p=0.001$), age ($p<.0001$), PSA lab values ($p<.0001$), SEER registry ($p<.0001$), poverty level ($p<.0001$), education ($p<.0001$), and marital status ($p=0.045$) (Table 3). Individuals harboring significant cancer on pathologic examination of the prostatectomy specimen were more likely to be non-white, of older age and unmarried. A larger percentage were

found in the west region and based on area measures of socioeconomic status they tended to reside at the time of diagnosis in locations with lower education and higher poverty. Clinically, a larger proportion of the group with significant cancer had PSA lab values greater than 5ng/ml. Observed differences were insignificant for sequence number (p=0.8204) and insurance status (p=0.2786)

Multivariate logistic regression analysis was conducted and the results are presented in Table 4. The outcome again was significant cancer based on results of the prostatectomy controlling for other covariates in the model. In the reduced model, we found that older age at diagnosis was a significant predictor of the outcome for all age groups: 55-59 yrs (OR=1.10, 95%CI: 1.00-1.21, p=0.042), 60-64 yrs (OR=1.23, 95%CI: 1.13-1.35, p<.0001) and 65+ yrs (OR=1.41, 95%CI: 1.28-1.54, p<.0001). African Americans had a 20% increased odds of significant cancer (OR=1.20, 95%CI: 1.09-1.33, p=0.0004) relative to whites, while individuals residing in the south region experienced a protective effect relative to those living in the west (OR=0.83, 95%CI: 0.76-0.91, p<.0001). Increasing PSA lab values were all predictors of significant PCa. Odds ratios in the various subgroups were as follows: 5-10ng/ml (OR=1.34, 95%CI: 1.25-1.44, p<.0001), 10-20ng/ml (OR=1.71, 95%CI: 1.51-1.94, p<.0001), and 20+ng/ml (OR=1.38, 95%CI: 1.15-1.67, p=0.0007). The “unknown” subgroup, which includes patients that have their test ordered but results were not in chart, or PSA lab values were not documented in patient record or unknown, was not statistically significant (p=0.095). Individuals residing in areas with census tract poverty in the range of 10%-20% were at increased odds of significant cancer (OR=1.33, 95%CI:

1.02-1.72, p=0.034) relative to the lowest poverty group. Similar results were observed for those in the highest poverty group (OR=1.28, 95%CI: 0.97-1.69, p=0.085), although the results did not reach significance.

DISCUSSION

With the widespread utilization of PSA testing for prostate cancer, more and more patients are being diagnosed with very early stage, clinically insignificant disease. Research has shown that a proportion of these patients' cancers are in fact more advanced at the time of diagnosis than originally thought. What is needed is a mechanism to more accurately distinguish these significant cancers at diagnosis from the truly insignificant ones. Since significant cancers are generally more aggressive than insignificant ones and more likely to cause death, it is important for clinicians to accurately classify patients clinically prior to treatment so that more informed decision making can take place regarding treatment. In this study, we assessed and identified a series of predictive factors that may help to better understand patient subpopulations at risk for harboring more significant disease than originally thought based on clinical examination alone.

Our study outcome was divided into two groups: cancers remaining insignificant following prostatectomy and cancers that were no longer insignificant. The study cohort started with PCa patients that were all clinically insignificant based on our local definition using available SEER data. We sought to examine potential factors that could predict the upgrade of Gleason score or the upstage of AJCC T stage from biopsy to prostatectomy. In the existing literature, there are only a few studies focused on both of these criteria (28, 29). Most studies were about examining predictors of GS upgrading, although the discrepancy between biopsy GS and prostatectomy GS should be properly assessed (23). For example, D'Amico et al assessed potential

predictors for GS grade 4 and 5 at prostatectomy in patients who had a biopsy Gleason grade of 3 or lower. In this study, however, they did not include information about possible extension of the cancer beyond the organ itself. Although managing prostate cancer is heavily based on GS, AJCC stage is important to consider in order to provide clinicians a broader view of the disease. The study by Chun et al also focused on upgrade of GS, but they included AJCC stage T3 in their cohort definition (30). Our study differs from the past ones in that our initial cohort did not contain any patient with a T stage that is greater than T2 and it focused on changes of both GS and AJCC T stage.

We demonstrated that patients with clinically insignificant prostate cancer have a higher propensity of harboring significant diseases if they have PSA lab values that are greater or equal to 5ng/ml. When the PSA lab value was between 10-20ng/ml, the odds of significant disease was 1.71 times higher than that of the range 0-5ng/ml. Other studies have demonstrated the fact that a high PSA lab value is a predictor of high-grade disease (24, 31). Seisen et al discovered that PSA>15ng/ml has a strong predictive effect on GS upgrading (24). This result is generally in accordance with the findings of our work. However, Seisen et al failed to demonstrate any predictive effect of a PSA lab value lower than 15ng/ml, which is different from our study. There are several reasons that can possibly explain the discrepancy. The first reason is that Seisen et al studied a sample size of 1,179 patients, while our study cohort contained 15,489 eligible patients. Larger sample sizes afford the opportunity to observe smaller differences. Secondly, the outcomes of these two studies differ from each other.

Although both outcomes can reflect the deterioration of the disease, the outcome of Seisen's study is the upgrade of GS, not the combination of changes of GS and AJCC T stage. Thirdly, PSA values were categorized differently. Seisen et al divided PSA values into four groups: 0-5ng/ml, 5-10ng/ml, 10-15ng/ml, and 15+ ng/ml, which differ from our study (0-5ng/ml, 5-10ng/ml, 10-20ng/ml, 20+ ng/ml, unknown). It could also make a difference how the starting cohort was defined. Seisen et al defined their cohort as biopsy GS<=6, T stage<=T2b, and preoperative PSA<=20ng/ml, which is different from our criteria.

Black race was another factor with a predictive effect on the outcome. As far as we know, there are limited studies that have focused on the predictive effect on the change of insignificant PCa to significant PCa following prostatectomy. However, there are similar studies. Hoffman et al found that clinically advanced-stage prostate cancers were detected more frequently in individuals with race classified as black compared to non-Hispanic white (32). In 2008, Jones et al also discovered that African-American men were significantly more likely than white men to have prostate cancers that had progressed beyond a localized stage (33). He attributed this result to the relatively lower socioeconomic status (SES) of African-American men. Higher SES may lead to the receipt of better medical care including a more thorough work-up during the clinical exam. This in turn could result in more accurate clinical test results. This may also explain part of our results. Further research is warranted to more fully understand the underlying reason for this racial difference observed in our study.

Age at diagnosis was also a predictive factor demonstrated in our study. We found that patients diagnosed at an age greater than 65 yrs had the highest risk of becoming significant cancer after prostatectomy. These results are in general agreement with others found in the literature. Lee et al found that patients aged>=70 yrs have a trend towards higher prostatectomy GS and higher AJCC stage compare to younger patients, but this was not significant on multivariate analysis (28). In this study, Lee et al categorized age into two subgroups: age>=70 yrs and age<70 yrs. Seisen et al also demonstrated the predictive effect of age on the outcome and showed that patients aged from 60-70 yrs and >=70 yrs were predictors of GS upgrade (24). Although the outcome of this study did not contain changes of AJCC stage, it shows similar results to our study.

While PSA and age were the strongest predictors, we also found that patients from the southern SEER regions of the US were protective of the outcome relative to those from the western SEER regions. This could be due to a variety of factors including regional differences in diagnostic practices, clinical workup, or pathologic evaluation of prostatectomy results. Further research is needed to fully understand the reason for these observed differences. We also found that area-based poverty was another predictor. Research has shown that people or families in poverty tend to receive less medical care. Possible access to care issues could also result in a less than thorough clinical exam which may lead to inaccuracy of the initial diagnosis. To our knowledge, no study has ever demonstrated any association between SEER registry, poverty and PCa upgrade or upstage.

Our study has its limitations. One of them is that we did not strictly follow the definition of clinically insignificant prostate cancer that is widely accepted because information on prostate volume does not exist in SEER data. Another limitation is that the study utilized an existing dataset of population-based cancer registry data. These data were collected in the field by a variety of different registrars with varying degrees of experience without external validation against medical records. In addition, all measurements of data are prone to inherent bias, especially in the absence of measurement validation through repeated measures. This may be due to imperfect calibration of measurement instruments, changes of environment that may interfere with measurement, or inaccurate observations from data collector. Finally, all patients in our cohort had a prostatectomy. Compared to other clinically insignificant PCa patients, it is possible that clinicians might have had additional information, which we could not obtain, that could have driven the choice for prostatectomy. In spite of these limitations, we feel that our methodology is sound and our results important. We have provided epidemiologists a series of demographic and clinical factors that can help to better understand patient subpopulations at risk for harboring more significant disease than originally thought based on clinical examination alone.

CONCLUSIONS

Patients diagnosed with clinically insignificant prostate cancer may harbor more significant cancer. We found that age at diagnosis and PSA lab value were two of the strongest predictors of significant PCa following prostatectomy. Race, SEER region and poverty were also independent predictors of PCa upgrade and upstage for selected groups. Of the entire cohort containing 112,475 PCa patients, 44,347 (39%) patients were diagnosed as clinically insignificant based on the result of biopsy. Of these clinically insignificant PCa patients, 15,892 had a prostatectomy and 8010 (50.4%) were subsequently classified as significant based on the result of prostatectomy. In addition, there were 28,455 patients with insignificant cancers at biopsy who did not undergo surgery. If our findings from this study were to extrapolate to this cohort, we would expect 14,341 (50.4%) of them to potentially harbor more significant cancer. In order to minimize or avoid misclassification, clinicians should try to increase the accuracy of clinical measurements in selected subgroups so that more informed decision making can take place.

FUTURE DIRECTIONS

In this study, we defined significant prostate cancer after prostatectomy as Gleason score greater than 6 (or with any grade 4 or 5) and/or a pathologic AJCC stage greater than T2. In the future studies, one could redefine the outcome in alternate ways. For example, the outcome could be more restrictive to only include prostatectomy GS greater than 6 (or with pattern 4 or 5) and an AJCC T stage greater than T2. One could then explore predictors of both upgrade and upstage simultaneously. The outcome could also be redefined as either upgrade or upstage alone to explore predictors of each individual component. Most importantly, future work should look for ways to improve the accuracy of clinical measurements so that clinicians can minimize the probability of misclassification and more accurately classify patients prior to treatment so that more informed decision making can take place.

REFERENCES

1. Fillmore RA, Kojima C, Johnson C, Kolcun G, Dangott LJ, Zimmer WE. New concepts concerning prostate cancer screening. Exp Biol Med (Maywood) 2014.

2. Xia T, Blackburn WR, Gardner WA, Jr. Fetal prostate growth and development. Pediatr Pathol 1990;10(4):527-37.

3. Allen KS, Kressel HY, Arger PH, Pollack HM. Age-related changes of the prostate: evaluation by MR imaging. AJR Am J Roentgenol 1989;152(1):77-81.

4. Cancer Facts & Figures 2012. In: Society AC, editor.; 2012.

5. Song SH, Pak S, Park S, Song C, Jeong IG, Choi HJ, et al. Predictors of Unfavorable Disease after Radical Prostatectomy in Patients at Low Risk by D'Amico Criteria: Role of Multiparametric Magnetic Resonance Imaging. J Urol 2014.

6. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360(13):1320-8.

7. Force USPST. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149(3):185-91.

8. Xu J, Zheng SL, Isaacs SD, Wiley KE, Wiklund F, Sun J, et al. Inherited genetic variant predisposes to aggressive but not indolent prostate cancer. Proc Natl Acad Sci U S A 2010;107(5):2136-40.

9. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin 2010;60(2):70-98.

10. Hu JC, Gu X, Lipsitz SR, Barry MJ, D'Amico AV, Weinberg AC, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. JAMA 2009;302(14):1557-64.

11. Elliott SP, Meng MV, Elkin EP, McAninch JW, Duchane J, Carroll PR, et al. Incidence of urethral stricture after primary treatment for prostate cancer: data From CaPSURE. J Urol 2007;178(2):529-34; discussion 534.

12. Litwin MS. Health related quality of life in older men without prostate cancer. J Urol 1999;161(4):1180-4.

13. Suardi N, Capitanio U, Chun FK, Graefen M, Perrotte P, Schlomm T, et al. Currently used criteria for active surveillance in men with low-risk prostate cancer: an analysis of pathologic features. Cancer 2008;113(8):2068-72.

14. Institute NC. NCI Dictionary of Cancer Terms. In.

15. Conti SL, Dall'era M, Fradet V, Cowan JE, Simko J, Carroll PR. Pathological outcomes of candidates for active surveillance of prostate cancer. J Urol 2009;181(4):1628-33; discussion 1633-4.

16. Ploussard G, Salomon L, Xylinas E, Allory Y, Vordos D, Hoznek A, et al. Pathological findings and prostate specific antigen outcomes after radical prostatectomy in men eligible for active surveillance--does the risk of misclassification vary according to biopsy criteria? J Urol 2010;183(2):539-44.

17. Suardi N, Briganti A, Gallina A, Salonia A, Karakiewicz PI, Capitanio U, et al. Testing the most stringent criteria for selection of candidates for active surveillance in patients with low-risk prostate cancer. BJU Int 2010;105(11):1548-52.

18. Shaw GL, Thomas BC, Dawson SN, Srivastava G, Vowler SL, Gnanapragasam VJ, et al. Identification of pathologically insignificant prostate cancer is not accurate in unscreened men. Br J Cancer 2014;110(10):2405-11.

19. Stamey TA, Freiha FS, McNeal JE, Redwine EA, Whittemore AS, Schmid HP. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. Cancer 1993;71(3 Suppl):933-8.

20. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994;271(5):368-74.

21. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280(11):969-74.

22. Wolters T, Roobol MJ, van Leeuwen PJ, van den Bergh RC, Hoedemaeker RF, van Leenders GJ, et al. A critical analysis of the tumor volume threshold for clinically insignificant prostate cancer using a data set of a randomized screening trial. J Urol 2011;185(1):121-5.

23. Sarici H, Telli O, Yigitbasi O, Ekici M, Ozgur BC, Yuceturk CN, et al. Predictors of Gleason score upgrading in patients with prostate biopsy Gleason score </=6. Can Urol Assoc J 2014;8(5-6):E342-6.

24. Seisen T, Roudot-Thoraval F, Bosset PO, Beaugerie A, Allory Y, Vordos D, et al. Predicting the risk of harboring high-grade disease for patients diagnosed with prostate cancer scored as Gleason </= 6 on biopsy cores. World J Urol 2014.

25. Milonas D, Grybas A, Auskalnis S, Gudinaviciene I, Baltrimavicius R, Kincius M, et al. Factors predicting Gleason score 6 upgrading after radical prostatectomy. Cent European J Urol 2011;64(4):205-8.

26. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64(1):9-29.

27. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17(6):1471-4.

28. Richstone L, Bianco FJ, Shah HH, Kattan MW, Eastham JA, Scardino PT, et al. Radical prostatectomy in men aged >or=70 years: effect of age on upgrading, upstaging, and the accuracy of a preoperative nomogram. BJU Int 2008;101(5):541-6.

29. Park HJ, Ha YS, Park SY, Kim YT, Lee TY, Kim JH, et al. Incidence of upgrading and upstaging in patients with low-volume Gleason score 3+4 prostate cancers at biopsy: finding a new group eligible for active surveillance. Urol Int 2013;90(3):301-5.

30. Chun FK, Briganti A, Shariat SF, Graefen M, Montorsi F, Erbersdobler A, et al. Significant upgrading affects a third of men diagnosed with prostate cancer: predictive nomogram and internal validation. BJU Int 2006;98(2):329-34.

31. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2006;98(8):529-34.

32. Hoffman RM, Gilliland FD, Eley JW, Harlan LC, Stephenson RA, Stanford JL, et al. Racial and ethnic differences in advanced-stage prostate cancer: the Prostate Cancer Outcomes Study. J Natl Cancer Inst 2001;93(5):388-95.

33. Jones BA, Liu WL, Araujo AB, Kasl SV, Silvera SN, Soler-Vila H, et al. Explaining the race difference in prostate cancer stage at diagnosis. Cancer Epidemiol Biomarkers Prev 2008;17(10):2825-34.

TABLES AND FIGURES

Figure 1. Figure of Exclusion on Study Cohort

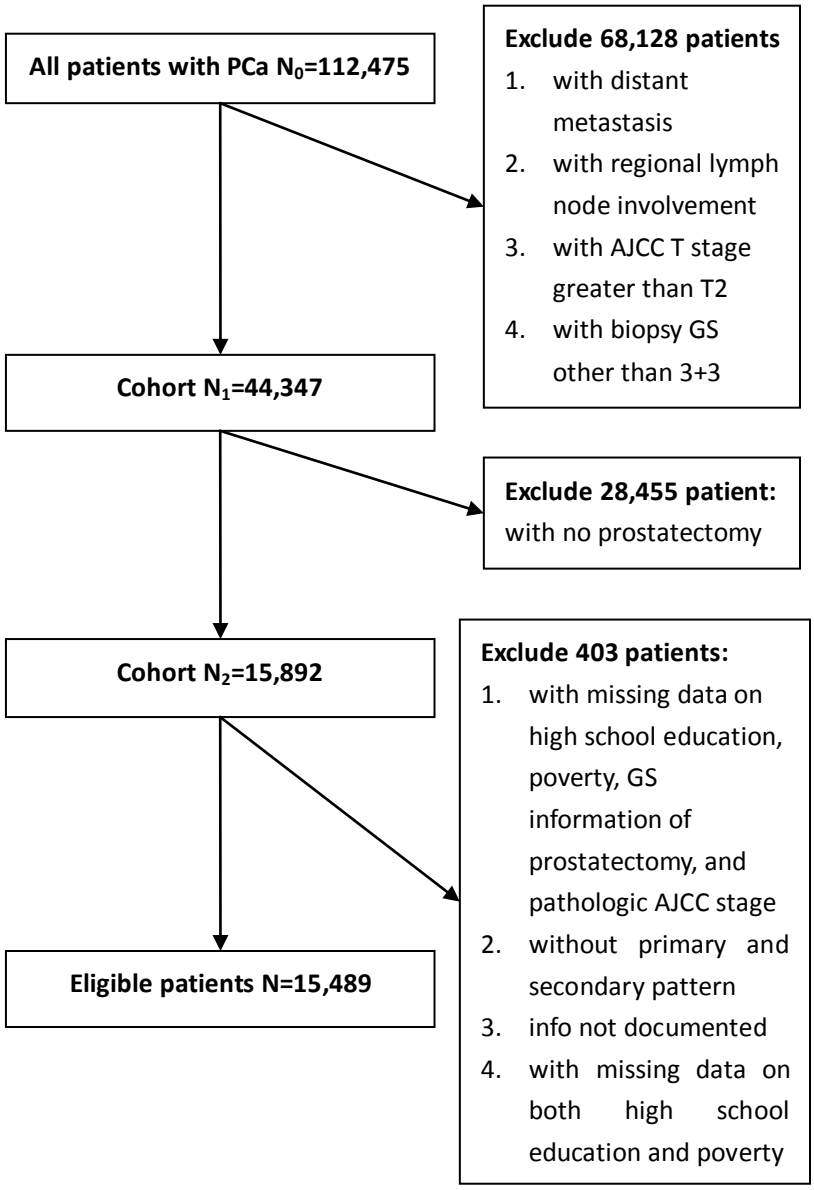

Table 1. Biopsy Gleason Score of PCa Patients by Biopsy T Stage

	Biopsy AJCC T Stage	
	T1-T2	T3-T4
Biopsy GS		
2-5	538(0.48%)	4(0.004%)
6	45,487(40.4%)	202(0.18%)
3+3	44,347(39.4%)	193(0.17%)
*Unknown	1,134(1.01%)	8(0.007%)
7	35,694(31.7%)	754(0.67%)
8	7679(6.83%)	428(0.38%)
9	4207(3.74%)	447(0.40%)
10	400(0.36%)	78(0.07%)

*****Primary and secondary patterns unknown

Table 2. Results of Prostatectomy by Prostatectomy Gleason Score and AJCC T Stage

	AJCC T Stage	
	T1-T2	T3-T4
Prostatectomy GS		
<=6 and without 4 or 5	7479(48%)	1228(8%)
>=7 or with 4 or 5	4647(30%)	2135(14%)

Table 3. Demographic and Clinical Features of Study Population by Results of Prostatectomy

	Prostatectomy Results				
Covariates	**Insignificant (0)**		**[1]Significant (1)**		
	N	Col %	N	Col %	
Number of patients	7479	48.29	8010	51.71	**P value**
Race					**P=0.001**
White	5540	74.07	5761	71.92	
Black	844	11.28	1019	12.72	
Hispanic	5540	74.07	5761	71.92	
Unknown	303	4.05	361	4.51	
Others	124	1.66	97	1.21	
Age (yrs)					**P<.0001**
0-54	1870	25.00	1658	20.70	
55-59	1924	25.73	1889	23.58	
60-64	1864	24.92	2083	26.00	
65+	1821	24.35	2380	29.71	
Education					**P<.0001**
[2]PLHE<=10.5%	1997	26.70	1887	23.56	
10.5%<PLHE<=13.79%	1927	25.77	2003	25.01	
13.79%<PLHE<=20.15%	1773	23.71	2018	25.19	
PLHE>20.15%	1782	23.83	2102	26.24	
[3]PSA lab value (ng/ml)					**P<.0001**
0-5	3302	44.15	2924	36.50	
5-10	2813	37.61	3490	43.57	
10-20	483	6.46	781	9.75	
20+	213	2.85	269	3.36	
Unknown	668	8.93	546	6.82	
SEER registry					**P<.0001**
West	3633	48.58	4271	53.32	
Midwest	696	9.31	754	9.41	
North	1410	18.85	1318	16.45	
South	1740	23.27	1667	20.81	
Sequence number					**P=0.8204**
One primary only	6951	92.94	7437	92.85	
one or more primaries	528	7.06	573	7.15	
Insurance					**P=0.2786**
Private insurance	7011	93.74	7500	93.63	

Any Medicaid	192	2.57	225	2.81	
Insurance status unknown	190	2.54	177	2.21	
Uninsured	86	1.15	108	1.35	
Marital status					**P=0.045**
Married	5779	77.27	6080	75.91	
Others	1700	22.73	1930	24.09	
Poverty					**P<.0001**
[4]PBP<5%	146	1.95	116	1.45	
5%<= PBP <10%	1574	21.05	1458	18.20	
10%<= PBP <20%	4851	64.86	5465	68.23	
PBP >=20%	908	12.14	971	12.12	

1. Significant: significant PCa, defined as prostatectomy GS>=6, or w/grade 4 or 5, or prostatectomy T stage T3-T4.
2. PLHE: population less than high school education
3. PSA: Prostate-specific antigen
4. PBP: population below poverty

Table 4. Multivariate Logistic Regression Analysis of Predictors of Upgrade and Upstage After Prostatectomy

Full	OR	95% CI	P value	Reduced	OR	95% CI	P value
Education				**Race**			
PLHE<=10.5%(R)	1.00			White(R)	1.00		
10.5%<=PLHE<13.79%	1.07	0.97-1.18	0.195	Hispanic	1.03	0.92-1.16	0.575
13.79%<=PLHE<20.15%	1.12	1.01-1.26	0.040	Black	1.20	1.09-1.33	0.0004
PLHE>=20.15	1.13	1.00-1.27	0.049	Unknown	0.80	0.61-1.04	0.098
Age of diagnosis				Others	1.01	0.86-1.19	0.911
0-54(R)	1.00			**Age of diagnosis**			
55-59	1.10	1.01-1.21	0.038	0-54(R)	1.00		
60-64	1.24	1.13-1.36	<.0001	55-59	1.10	1.00-1.21	0.042
65+	1.42	1.29-1.55	<.0001	60-64	1.23	1.13-1.35	<.0001
Race				65+	1.41	1.28-1.54	<.0001
White(R)	1.00			**PSA lab value**			
Hispanic	1.01	0.90-1.14	0.838	0-5(R)	1.00		
Black	1.18	1.07-1.31	0.002	5-10	1.34	1.25-1.44	<.0001
Unknown	0.79	0.60-1.03	0.082	10-20	1.71	1.51-1.94	<.0001
Others	1.00	0.85-1.18	0.964	20+	1.38	1.15-1.67	0.0007
PSA lab value				Unknown	0.90	0.79-1.02	0.095
0-5(R)	1.00			**SEER registry**			

5-10	1.34	1.24-1.43	<.0001	West(R)	1.00		
10-20	1.70	1.50-1.93	<.0001	Midwest	1.01	0.90-1.14	0.878
20+	1.37	1.14-1.66	0.0009	North	0.95	0.86-1.04	0.270
Unknown	0.90	0.79-1.02	0.095	South	0.83	0.76-0.91	<.0001
SEER registry				**Poverty**			
West(R)	1.00			PBP<5%(R)	1.00		
Midwest	1.04	0.92-1.18	0.516	5%<=PBP<10%	1.12	0.86-1.46	0.394
North	0.95	0.86-1.05	0.353	10%<=PBP<20%	1.33	1.02-1.72	0.034
South	0.84	0.77-0.92	0.0001	PBP>=20%	1.28	0.97-1.69	0.085
Sequence number							
1 primary only(R)	1.00						
>=1 primary	1.00	0.88-1.13	0.946				
Insurance							
All insured(R)	1.00						
Any Medicaid	0.98	0.80-1.19	0.811				
Unknown	0.95	0.76-1.18	0.617				
Uninsured	1.16	0.87-1.55	0.311				
Marital status							
Married(R)	1.00						
Others	1.06	0.99-1.15	0.116				
Poverty							
PBP<5%(R)	1.00						
5%<=PBP<10%	1.09	0.83-1.42	0.551				
10%<=PBP<20%	1.21	0.92-1.59	0.183				
PBP>=20%	1.12	0.83-1.51	0.468				