Critical assessment of prebiopsy parameters for predicting prostate cancer metastasis and mortality

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Introduction: *Value of characteristics assessed prior to diagnosis predicting aggressive prostate cancer, metastases and mortality in men participating in a screening study were identified.*

Materials and methods: *This study included 19950 men, aged 55 to 74 years at first screening, in the European Randomized Study of Screening for Prostate Cancer. Age, Charlson comorbidity, prostate cancer family history, vasectomy status, International Prostate Symptom Score (IPSS) score, digital rectal examination (DRE) status, transrectal ultrasound (TRUS) findings, prostate volume and prostate-specific antigen (PSA) level were assessed. Men were followed for median 11.1 years after first screening visit. Multivariate estimates of the probability of aggressive prostate cancer [stage ≥ T2c, or N1, M1, PSA > 20 ng/mL, or Gleason score ≥ 8], developing distant metastases and dying from prostate cancer stratified for predictors measured before prostate biopsies. Harrell's concordance index (c-index) was used for predictive accuracy.*

Results: *Among 19950 men, 2420 men (12.1%) were diagnosed with prostate cancer, of which 623 men (3.1%) had aggressive prostate cancer, 157 men (0.8%) developed metastases and 104 men (0.5%) died due to a prostate cancer related cause of death. In multivariate analysis, PSA, DRE, TRUS findings and prostate volume had a significant association with detection of aggressive prostate cancer, metastases and prostate cancer mortality. Family history was significantly associated with aggressive prostate cancer. Accuracy for predicting aggressive prostate cancer c-index = 0.90, distant metastases c-index = 0.87, and prostate cancer specific mortality c-index = 0.87.*

Conclusions: *In a large population of men who were screened for prostate cancer, detection of aggressive prostate cancer, metastases and prostate cancer mortality was predicted based on predictors available before biopsy. These results support the value of a multivariate risk assessment and stratification tools.*

Key Words: prostate cancer, PSA, screening, early detection, DRE, risk

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Introduction

Population based screening has the potential to reduce prostate cancer mortality.[1-3] Screening increases the prostate cancer incidence, and has shifted the diagnosis to an earlier point in time. Consequently, many men are diagnosed with screen detected prostate cancer that would not have led to symptoms or death during life and therefore would not have been diagnosed clinically (overdiagnosis).

To decrease the rate of overdiagnosis, improvements of screening and early detection strategies are needed. Therefore, the characterization and identification of indolent prostate cancer, clinically significant prostate cancer and potentially lethal prostate cancer is essential.

This study assessed the association between the prebiopsy characteristics and aggressive prostate cancer, prostate cancer metastases and prostate cancer specific mortality in a contemporary cohort of men participating in the intervention arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam.

Materials and methods

Between December 1993 and December 1999, a total of 21175 men, aged 55-74 year were randomized to the intervention arm of the ERSPC-Rotterdam. A total of 19950 men (94.2%) were actually screened. Between 1993 and May 1997 men were screened with an interval of 4 years by prostate-specific antigen (PSA) measurement, digital rectal examination (DRE) and transrectal ultrasound (TRUS) examination. Sextant biopsy was initially offered to men with PSA ≥ 4.0 ng/mL and/or suspicious finding on DRE and/or TRUS. After May 1997 a biopsy was prompted by PSA ≥ 3.0 ng/mL only. From June 1996 on, transrectal sextant biopsies were carried out in the more lateral peripheral zone.[4] Treatment decisions were made by a local urologist in consultation according to patients preference. The details of the screening methodology were previously described.[5] Cancers diagnosed between the screening intervals or after the age of 74 years, were considered as well. These cancers were identified by linkage to the national cancer registry. All cancers were classified according to the primary TNM classification of 1992. A potentially life-threatening aggressive cancer was defined as a high risk prostate cancer based on the classification presented by D'Amico et al.[6] In this study, high risk patients were considered as aggressive cancers, with N1 and M1 cases added to the aggressive cancer group. Presence of distant metastasis was defined by a positive isotope bone scan, or by a serum PSA concentration ≥ 100.0 ng/mL, when an isotope bone scan was not performed. Patients with positive lymph nodes but a negative isotope bone scan were considered as M0. Causes of death were based on the consensus of a Causes of Death Committee (CODC) that reviewed all deceased men with prostate cancer using a predefined decision tree.[7]

Predictors prior to diagnosis

The included predictors were age, Charlson comorbidity score, prostate cancer family history, the vasectomy status, International Prostate Symptom Score (IPSS), DRE status, findings on TRUS, prostate gland volume and serum PSA level. Information on family history, lower urinary tract symptoms and comorbidities were obtained by a self-administered questionnaire at study entry. A positive family history was defined as having a father and/or one or several brothers diagnosed with prostate cancer. TRUS was performed using a Bruel & Kjaer, Glostrup, Denmark model1846 mainframe and a 7-MHz biplanar endorectal transducer. Hypoechoic lesions were considered suspicious. The prostate gland volume was obtained through a planimetric volume measurement with a 0.5 cm step section by TRUS.

Statistical analysis

Diagnostic and mortality data were available until December 31, 2008. Consequently, date of censoring was at emigration or December 31, 2008. The predictors assessed during the first screening round were compared between men who respectively were diagnosed with aggressive prostate cancer, developed prostate cancer metastases, died from prostate cancer and men who did not suffer any of these events. The duration of follow up was computed for all participants from the time of first screening visit until the event of interest, date of death, or December 31, 2008, whichever occurred first.

Two multivariate models were fitted. In the first model, age, Charlson comorbidity score, prostate cancer family history, vasectomy status, IPSS score, DRE and serum PSA (logarithm transformed) were included (i.e. the limited model from here on). Subsequently, the advanced model was fitted by adding the prostate gland volume (logarithm transformed) and the findings on TRUS to the limited model. The hypothesis to perform a limited and an advanced model was related to two moments in the early detection process and risk assessment of prostate cancer. The first moment affects the first regular consult with the physician. The second moment considers the time that additional information is obtained from TRUS. All men were contributing to each model since missing values of predictors were replaced by an indicator. Outcomes in prostate cancer metastases and prostate cancer death were adjusted for the difference in primary treatment modalities (i.e., surgery, radiotherapy, watchful waiting/active surveillance and hormone treatment).

The multivariate models were based on Cox proportional hazards regression model with the time of follow up from first screening until either the event of interest or censoring. A time dependent covariate approach was used to estimate the hazard ratios (HR) for prostate cancer metastasis and death adjusted for the difference in treatment. Treatment was included as a time dependent covariate from the time of diagnosis until the event of interest, date of death, or December 31, 2008, whichever occurred first. The results were shown as HR with 95% confidence intervals (95% CI). The assumption of proportionality was tested through the

construction of log-minus-log and smooth Schoenfeld residual plots, both of which demonstrated essentially parallel curves. For each multivariate model, Harrell's concordance index (c-index) was calculated as a measure of predictive accuracy. Interpretation of the c-index is similar to that of the area under a receiver operating characteristic curve for a diagnostic test; a c-index of 0.5 indicates that the instrument does no better than random guessing and a c-index of 1.0 indicates 100% predictive accuracy. P values less than 0.05 were considered to be statistically significant. All analyses were performed with STATA, version 11.0.

Results

Baseline characteristics

This retrospective study included a total of 19950 predominantly white men, median age 63 years, were included in this study population. The characteristics at study entry are presented in Table 1. Up to the end of 2008, a total of 2420 men (12.1%) were diagnosed with prostate cancer. Median follow up was 11.1 years.

Aggressive prostate cancer

Total of 623 (3.1%) men were diagnosed with aggressive prostate cancer. Univariate associations between the prebiopsy predictors and the detection of aggressive cancer are presented in Table 2. In the limited multivariate model, serum PSA (HR 3.37, 95% CI 3.14-3.62), positive DRE (HR 5.84, 95% CI 4.87-7.00) and a positive family history (HR 1.92, 95% CI 1.47-2.49) were significantly associated with the diagnosis of aggressive prostate cancer. In the advanced model serum PSA, positive DRE, prostate volume, positive TRUS and a positive family history were significantly associated with the detection of aggressive prostate cancer, Table 2. Predictive accuracy was good for both models; for the limited and advanced model c-index = 0.90.

Prostate cancer metastasis

Total of 153 (0.8%) men were diagnosed with prostate cancer metastases during study observation. Univariate associations between the prebiopsy predictors and the development of prostate cancer metastases are presented in Table 3. In the limited multivariate model, serum PSA (ln) (HR 1.86, 95% CI 1.60-2.17) and a positive DRE (HR 2.82, 95% CI 1.92-4.13) were significantly associated with the diagnosis of metastasis. In the advanced model serum PSA, a positive DRE and the prostate volume were significantly associated with the development of metastasis. Predictive accuracy for the models was: c-index = 0.86 for the limited model and c-index = 0.87 for the advanced model.

TABLE 1. **Characteristics of participants at study entry**

	Men, N (% of total)
Total participants	19950
Age (yr), median	63
55-60	7693 (38.6)
61-65	4216 (21.1)
66-70	4742 (23.8)
71-75	3299 (16.5)
PSA (ng/mL), median	1.3
0.0-2.9	16027 (80.4)
3.0-9.9	3478 (17.4)
10.0-19.9	318 (1.6)
≥ 20.0	127 (0.6)
DRE	
Positive	1569 (7.9)
Negative	8185 (41.0)
Unknown	10196 (51.1)
Family history prostate cancer	
Yes	1362 (6.8)
No	12944 (64.9)
Unknown	5644 (28.3)
Vasectomy	
Yes	5141 (25.8)
No	13959 (70.0)
Unknown	850 (4.2)
Charlson comorbidity score	
0	14612 (73.2)
1	4505 (22.6)
≥ 2	691 (3.5)
Unknown	142 (0.7)
IPSS, prostate symptom score	
Mild (IPSS of 0 to 7)	14155 (71.0)
Moderate (IPSS of 8 to 19)	4297 (21.5)
Severe (IPSS of 20 or more)	1032 (5.2)
Unknown	466 (2.3)

PSA = prostate specific antigen; IPSS = International Prostate Symptom Score; DRE = digital rectal examination

Prostate cancer death

A total of 104 (0.5%) men died from a prostate cancer related cause of death. Univariate associations between the prebiopsy predictors and the death from prostate cancer are presented in Table 4. In the limited multivariate model, serum PSA (ln) (HR 1.73, 95% CI 1.45-2.07) and a positive DRE (HR 2.50, 95% CI 1.59-3.95) were significantly associated with the death from prostate cancer. In the advanced model serum PSA, a positive DRE, a positive TRUS and low

TABLE 2. **Prebiopsy predictors for detection of aggressive prostate cancer**

Variable	Aggressive prostate cancer Univariate analyses		Aggressive prostate cancer Multivariate analyses	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age	1.08 (1.07-1.10)	< 0.001	1.04 (1.02-1.06)	< 0.001
PSA (ln)	4.23 (3.98-4.40)	< 0.001	3.25 (3.00-3.53)	< 0.001
DRE				
Negative	*		*	
Positive	10.04 (8.45-11.92)	< 0.001	3.65 (2.98-4.47)	< 0.001
Prostate volume (ln)	1.40 (1.14-1.71)	0.001	0.30 (0.23-0.38)	< 0.001
TRUS				
Negative	*		*	
Positive	8.50 (7.18-10.07)	< 0.001	2.76 (2.25-3.38)	< 0.001
Family history				
Negative	*		*	
Positive	1.76 (1.36-2.29)	< 0.001	1.67 (1.26-2.22)	< 0.001
Charlson comorbidity				
0	*		*	
1	1.20 (0.99-1.44)	0.053	1.01 (0.82-1.24)	0.913
≥ 2	1.16 (0.76-1.78)	0.490	1.22 (0.76-1.98)	0.408
Vasectomy				
No	*		*	
Yes	0.83 (0.68-1.00)	0.051	1.20 (0.97-1.49)	0.099
IPSS score				
Mild	*		*	
Moderate	1.00 (0.82-1.21)	0.978	0.75 (0.61-0.93)	0.009
Severe	1.16 (0.83-1.63)	0.385	0.90 (0.62-1.32)	0.603

PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound; IPSS = International Prostate Symptom Score; ln = logarithm transformed
*reference group to which other groups are compared. The reference group per definition has a hazard ratio of 1.

prostate volume were significantly associated with the death from prostate cancer. Predictive accuracy for the limited and advanced model was c-index = 0.87.

Discussion

This study provides information on the predictive value of clinical characteristics available before a prostate biopsy. The characteristics with significantly predictive value for the detection of aggressive prostate cancer were in line with those predicting the development of distant metastases and death from prostate cancer.

Screening aims to identify significant or to-be significant prostate cancer at a stage where treatment can be applied to prevent death or suffering. For prostate cancer this seems to be an appealing option due to the natural history of prostate cancer with a relative long period in which prostate cancer is recognizable and detectable in a localized stage (window of curability). Overdiagnosis with the related overtreatment is the most important side effect of an early detection program for prostate cancer by now.[8] Therefore, experts support the need of a marker or early detection strategy that only identifies the clinical relevant prostate cancer. Our findings are in line with previous studies showing that a combination of factors is sensitive for the detection of (aggressive) prostate cancer.[9-11] The only controversy between the outcomes of our study and the aim of screening is that this study identifies the prebiopsy characteristics predicting outcomes in men in whom screening has

TABLE 3. **Prebiopsy predictors for detection of prostate cancer metastases**

Variable	Prostate cancer metastasis Univariate analyses		Prostate cancer metastasis Multivariate analyses	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age	1.12 (1.08-1.15)	< 0.001	1.00 (0.97-1.04)	0.863
PSA (ln)	4.27 (3.81-4.78)	< 0.001	1.93 (1.61-2.32)	< 0.001
DRE				
Negative	*		*	
Positive	10.12 (7.10-14.42)	< 0.001	2.35 (1.53-3.62)	< 0.001
Prostate volume (ln)	1.71 (1.13-2.59)	0.093	0.50 (0.31-0.80)	0.004
TRUS				
Negative	*		*	
Positive	7.30 (5.18-10.29)	< 0.001	1.42 (0.92-2.20)	0.140
Family history				
Negative	*		*	
Positive	2.06 (1.26-3.38)	0.004	1.53 (0.87-2.74)	0.117
Charlson comorbidity				
0	*		*	
1	1.55 (1.10-2.20)	0.013	1.40 (0.94-2.09)	0.097
≥ 2	1.05 (0.39-2.85)	0.921	0.30 (0.07-1.37)	0.122
Vasectomy				
No	*		*	
Yes	0.74 (0.51-1.10)	0.136	1.09 (0.69-1.73)	0.695
IPSS score				
Mild	*		*	
Moderate	1.42 (0.99-2.03)	0.053	1.26 (0.85-1.87)	0.248
Severe	1.44 (0.75-2.72)	0.267	1.83 (0.86-3.90)	0.118

PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound; IPSS = International Prostate Symptom Score; ln = logarithm transformed
*reference group to which other groups are compared. The reference group per definition has a hazard ratio of 1.

failed (i.e., distant metastases and prostate cancer death). Still these findings are important for the improvement of early detection programs. It prooves that algorithms that detect potentially life-threatening disease are an option, and identifies the prebiopsy characteristics that should at least be included in early detection algorithms that have the aim to detect clinically significant cancers. Additional validation is needed to assess the appropriate cut off values for these multivariate screening strategies. Consequently, it would be desirable to add more prebiopsy markers with significant additional value to our model to increase the value of early detection strategies to selectively detect aggressive and indolent cancers.

PSA, DRE, findings on TRUS and the prostate volume contribute significantly to all predictive models. Based on the Harrell's concordance index little to no additional predictive accuracy was observed for the advanced relative to the limited model. This might increase the clinical usefulness since a good prediction seems to be possible without using TRUS. Data showed that DRE remains of value in the individualized risk stratification. These observations are in line with studies that developed risk strategies with the potential to decrease the probability of having an indolent cancer and those that showed a more frequent detection of potentially aggressive prostate cancer (Gleason score ≥ 7) in men who had an abnormal DRE.[10,12] Present study adds additional evidence that men with smaller prostate glands have worse outcomes with respect to prostate cancer metastases and prostate cancer specific mortality. This

TABLE 4. **Prebiopsy predictors for prostate cancer mortality**

Variable	Prostate cancer specific death Univariate analyses		Prostate cancer specific death Multivariate analyses	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age	1.14 (1.10-1.18)	< 0.001	1.02 (0.98-1.07)	0.360
PSA (ln)	3.81 (3.36-4.31)	< 0.001	1.68 (1.36-2.07)	< 0.001
DRE				
Negative	*		*	
Positive	9.14 (6.90-13.92)	< 0.001	2.12 (1.26-3.55)	0.004
Prostate volume (ln)	1.54 (0.93-2.57)	0.093	0.50 (0.28-0.90)	0.020
TRUS				
Negative	*		*	
Positive	7.42 (4.91-11.23)	< 0.001	1.72 (1.01-2.90)	0.044
Family history				
Negative	*		*	
Positive	1.34 (0.67-2.70)	0.405	1.14 (0.56-2.34)	0.711
Charlson comorbidity				
0	*		*	
1	1.74 (1.19-2.66)	0.013	1.60 (1.03-2.49)	0.038
≥ 2	1.28 (0.40-4.06)	0.921	0.88 (0.20-3.87)	0.868
Vasectomy				
No	*		*	
Yes	0.56 (0.33-0.95)	0.032	0.79 (0.45-1.40)	0.429
IPSS score				
Mild	*		*	
Moderate	1.14 (0.72-1.81)	0.574	0.91 (0.55-1.52)	0.718
Severe	1.25 (0.54-2.89)	0.593	1.04 (0.39-2.77)	0.943

PSA = prostate-specific antigen; DRE = digital rectal examination; TRUS = transrectal ultrasound; IPSS = International Prostate Symptom Score; ln = logarithm transformed
*reference group to which other groups are compared. The reference group per definition has a hazard ratio of 1.

is in line with strong and consistent evidence that men with smaller prostate gland volumes are at an increased risk of the detection of (aggressive) prostate cancer and at increased risk of clinically significant upgrading after radical prostatectomy.[13-15] This study observed no association of vasectomy, family history, comorbidity status, and urological symptoms with the development of distant metastases and death from prostate cancer. Although vasectomy has been associated with the risk of prostate cancer, recent studies have shown that confounders were likely responsible for these positive associations.[16,17] This is confirmed in the current study showing no relation between the vasectomy status, detection of aggressive prostate cancer, distant metastases and prostate cancer specific mortality. Men with a positive family history for prostate cancer were in multivariate analysis at an increased risk of diagnosis with aggressive prostate cancer, but not of developing distant metastases or dying from prostate cancer. The observations are in line with a population based study, including more than 11.8 million individuals, that showed an increased risk of diagnosis with prostate cancer and death from prostate cancer in men affected fathers and brothers in an univariate analysis.[18] Since the present study showed an increased risk for diagnosis with aggressive prostate cancer in a systematic screening trial and[18] showed that the risk of death from prostate cancer was increasing with the number of affected relatives we can conclude that the risk for men with affected relatives is not primary increased due to an increased surveillance among men with affected relatives.

The present outcomes might be limited by the difference in treatment. Adjustment was made by including the primary treatment as a time dependent covariate in the Cox regression analysis. No coefficients for treatment are reported in the model, since the performed primary treatments remain a decision by independent urologists and patients and are thus biased. Therefore, presented models should be interpreted as if all patients received the same primary treatment. Additional limitations worth to be mentioned are that most prebiopsy information remains subjective. Secondly, only men with their first screening up to May 1997 had real contributing data of DRE and TRUS since these data were standard routinely assessed in participants screened up to this date. No data on PSA kinetics was included although PSA kinetics have shown to be significantly associated with a shorter time to PC specific mortality.[19,20] No association was observed between the comorbidity status and the death from prostate cancer although comorbidity is an established strong determinant of survival among men with prostate cancer. A possible explanation for the limited observed results could be the selected healthy study population since only 3.5% of the participants reported a Charlson score ≥ 2 at first screening visit. Finally, it is debatable whether the use of a self-administered questionnaire is a reliable method for acquiring data on family history, lower urinary tract symptoms and comorbidities. Strengths of the study are that it is the first study analyzing these associations within a prostate cancer screening program and can form the basis for long term predictive models.

To the best of our knowledge, this is the first study showing that, in a large population of men who were screened and treated for prostate cancer, the detection of aggressive prostate cancer, metastases and death from prostate cancer could be predicted with good accuracy based on clinical parameters before biopsy. Serum PSA, DRE, findings on TRUS and prostate volume had all a significant contribution to the prediction of the outcomes of interest, family history was significantly associated with the detection of aggressive prostate cancer. The risk stratification is limited due to the potential bias of treatment. Harrell's concordance index showed roughly similar accurate prediction for the models that included and excluded the findings on TRUS. The results have important implications for future research and support the value of early detection strategies based on multiple clinical characteristics instead of PSA alone in order to reduce the most important side effects of prostate cancer screening. □

References

1. Schroder FH, Hugosson J, Roobol MJ et al. Screening and prostate cancer mortality in a randomized European study. *N Engl J Med* 2009;360(13):1320-1328.
2. Roobol MJ, Kerkhof M, Schroder FH et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur Urol* 2009;56(4):584-591.
3. Hugosson J, Carlsson S, Aus G et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 2010;11(8):725-732.
4. Eskew LA, Bare RL, McCullough DL. Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. *J Urol* 1997;157(1):199-202;discussion 202-203.
5. Roobol MJ, Schroder FH. European Randomized Study of Screening for Prostate Cancer: achievements and presentation. *BJU Int* 2003;92(Suppl 2):117-122.
6. D'Amico AV, Whittington R, Malkowicz SB et al. Predicting prostate specific antigen outcome preoperatively in the prostate specific antigen era. *J Urol* 2001;166(6):2185-2188.
7. De Koning HJ, Blom J, Merkelbach JW et al. Determining the cause of death in randomized screening trial(s) for prostate cancer. *BJU Int* 2003;92(Suppl 2):71-78.
8. Draisma G, Boer R, Otto SJ et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003;95(12):868-878.
9. Thompson IM, Ankerst DP, Chi C et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 2006;98(8):529-534.
10. Roobol MJ, Steyerberg EW, Kranse R et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Eur Urol* 2010;57(1):79-85.
11. Hernandez DJ, Han M, Humphreys EB et al. Predicting the outcome of prostate biopsy: comparison of a novel logistic regression-based model, the prostate cancer risk calculator, and prostate-specific antigen level alone. *BJU Int* 2009;103(5):609-614.
12. Okotie OT, Roehl KA, Han M, Loeb S, Gashti SN, Catalona WJ. Characteristics of prostate cancer detected by digital rectal examination only. *Urology* 2007;70(6):1117-1120.
13. van Leeuwen P, van den Bergh R, Wolters T, Schroder F, Roobol M. Screening: should more biopsies be taken in larger prostates? *BJU Int* 2009;104(7):919-924.
14. Briganti A, Chun FK, Suardi N et al. Prostate volume and adverse prostate cancer features: fact not artifact. *Eur J Cancer* 2007;43(18): 2669-2677.
15. Freedland SJ, Isaacs WB, Platz EA et al. Prostate size and risk of high-grade, advanced prostate cancer and biochemical progression after radical prostatectomy: a search database study. *J Clin Oncol* 2005;23(30):7546-7554.
16. Holt SK, Salinas CA, Stanford JL. Vasectomy and the risk of prostate cancer. *J Urol* 2008;180(6):2565-2567; discussion 2567-2568.
17. Stanford JL, Wicklund KG, McKnight B, Daling JR, Brawer MK. Vasectomy and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 1999;8(10):881-886.
18. Brandt A, Bermejo JL, Sundquist J, Hemminki K. Age-specific risk of incident prostate cancer and risk of death from prostate cancer defined by the number of affected family members. *Eur Urol* 2010;58(2):275-280.
19. D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004;351(2):125-135.
20. D'Amico AV, Renshaw AA, Sussman B, Chen MH. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. *JAMA* 2005;294(4):440-447.