Simple Risk Stratification to Detect Prostate Cancer with High Gleason Score in Repeat Biopsies in a Population Screening Follow-up Study

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Abstract. *Background: To investigate the clinical usefulness of percentage free prostate-specific antigen (%fPSA) and PSA velocity (PSAV) for detecting prostate cancer in repeat biopsies in a population-based screening cohort. Patients and Methods: In total, 178 men with serum PSA levels within 2.1-10 ng/ml who underwent repeat biopsies after initial negative biopsy results, were enrolled. Prostate cancer detection rates with a Gleason score of 7 or more according to age, serum PSA, %fPSA, and PSAV were investigated. The cumulative probability of detecting cancer according to risk factors was also investigated. Results: Out of 178 men who underwent repeat biopsy, 48 (27.0%) were diagnosed with prostate cancer during the observation period, and pathological examination revealed prostate cancer with a Gleason score of 7 or more in 17 patients (35.4%). In the multivariate logistic regression analysis, %fPSA ≤12 at repeat biopsy and PSAV >0.40 ng/ml/year were determined to be independent risk factors for prostate cancer, and %fPSA ≤12 at initial biopsy and PSAV >0.40 for cancer of Gleason score 7 or greater. The cumulative probabilities of developing high-grade cancer after 5 years were 55.8% and 4.0% in men with %fPSA ≤12 at initial biopsy and PSAV >0.40 , and in men without both, respectively. There was a statistically significant difference in probabilities between groups by the log-rank test. Conclusion: The present results demonstrated that %fPSA and PSAV were predictors of prostate cancer with a Gleason score of 7 or more in repeat biopsy after a negative initial biopsy on a population follow-up basis.*

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Key Words: prostate cancer, repeat biopsy, percentage free PSA, PSA velocity, population screening, Gleason score ≥7.

At present, prostate cancer is usually diagnosed based on the pathological examination of ultrasound-guided transrectal or transperineal core biopsy (1). The need for prostate biopsy is based on the presence of elevated serum prostate-specific antigen (PSA) and whether it is associated with the presence of abnormal digital rectal examination (DRE) findings. The management of candidates who have a negative result in the initial prostate biopsy may be a serious concern because negative biopsy results cannot guarantee the absence of prostate cancer (2-4). More than one-fourth of all prostate carcinomas are missed during the first biopsy, and several markers, including initial serum PSA, PSA kinetics, percentage of free PSA (fPSA), pathological findings in initial biopsy, and prostate volume, are significantly correlated with the detection of prostate cancer in repeat biopsies (5, 6). Previous studies have reported that a nomogram comprising of several risk factors (*e.g.*, PSA velocity (PSAV), %fPSA, DRE findings, PSA density, and history of abnormal pathological findings) may be useful for determining the indication for a repeat biopsy (4, 7, 8).

However, since these risk factors have been determined on an outpatient referral basis, an issue arose regarding appropriate follow-up in a population-based screening for men with a negative initial prostate biopsy (5). In such cases, simple markers, such as age, serum PSA, and PSA-related indices, should only be used for selecting screened patients who need a repeat biopsy.

In the present study, we investigated the clinical usefulness of serum PSA, %fPSA, and PSAV for detecting prostate cancer, especially that with high Gleason scores in repeat biopsies, on a population basis.

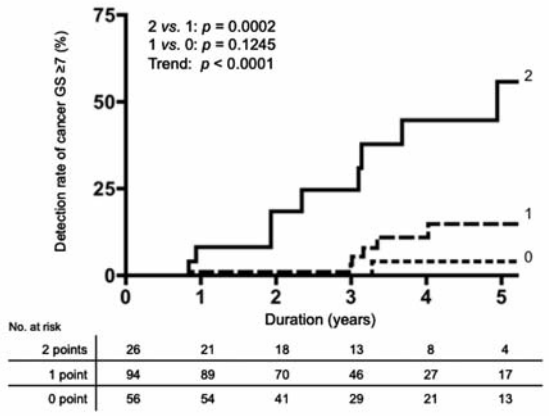

Figure 1. *Cumulative probability of developing prostate cancer with a Gleason score (GS) of 7 or greater during follow-up according to the percentage of free prostate-specific antigen (%fPSA) at initial biopsy and PSA velocity (PSAV). %fPSA ≤12 and PSAV >0.40 ng/ml/year were each scored as 1 point, and cases were then categorized into three groups with 2 points, 1 point, and 0 points, respectively.*

Patients and Methods

Study population. Since 2000, annual population PSA-based screening for prostate cancer has been provided for men aged 54-69 years in Kanazawa City, Japan (9, 10). Serum total PSA (tPSA) levels were measured in all participants using a Tosoh II PA kit (Tosoh, Tokyo, Japan) as the primary screening modality, and serum fPSA levels were measured in participants with tPSA levels within the range of 2.1-10.0 ng/ml using an Immulyze Free PSA kit (Nippon DPC Co. Ltd., Chiba, Japan). Between 2000 and 2002, participants with serum tPSA levels >2.0 ng/ml were recommended to undergo further examination by urologists at primary medical care level clinics. After 2003, participants with serum tPSA >10.0 ng/ml and those with %fPSA ≤22.0, within the PSA reflex range of 2.1-10.0 ng/ml, were recommended to proceed to closer examination (9, 10). Since 2012, the age range of participants has expanded to 54-75 years.

After closer examination by urologists, systematic transrectal ultrasound (TRUS)-guided prostate biopsy (8-12 cores) was basically recommended in men with any abnormal findings after re-evaluating PSA, DRE, or TRUS. If individuals disagreed with undergoing prostate biopsy or were not recommended to undergo biopsy by urologists, they would be followed-up by annual PSA tests at subsequent population screenings.

In cases of prostate cancer diagnosis, pathological tumor grading was reported by local pathologists, and clinical staging was determined according to the Union for International Cancer Control tumor node metastasis classification published in 1997 (11), based on the results of DRE, TRUS, computed tomography, magnetic resonance imaging (MRI), and bone scan at each urological department. Medical information, including PSA levels at the primary screening, biopsy results, and clinicopathological findings, was reported to the office of the Kanazawa Medical Association.

In the Kanazawa population-based cohort, 22,252 men participated in the 14-year screening program from 2000 to 2013, and 1,792 men (8.1%) underwent prostate biopsy during this period. Out of the 1,792 men, 499 (27.8%) were pathologically diagnosed with prostate cancer based on the initial biopsy results, and 247 (13.8%) underwent repeat biopsy after initial negative biopsy results. The indication for repeat biopsy was based on the decision of treating urologists; however, elevated serum PSA was used as the indicator in most cases. Of the men who underwent repeat biopsy, those with tPSA levels >10 ng/ml were excluded. Consequently, 178 men with tPSA levels of 2.1-10 ng/ml who underwent repeat biopsy after initial negative biopsy results were enrolled into the present study. We calculated PSAV as follows: [PSA (latest biopsy)−PSA (initial biopsy)]/number of years between PSA tests, and investigated the risk of detecting prostate cancer according to age, serum PSA level, %fPSA at biopsy, and PSAV. The time of the detection of prostate cancer was calculated from the date of the initial biopsy, and the men without evidence of cancer were censored at the date of the latest biopsy.

Statistical analysis. This retrospective study received Institutional Review Board approval (Kanazawa University 1558). Comparisons between two groups were performed using the Mann–Whitney *U*-test. The risk of prostate cancer detection was analyzed by univariate and multivariate logistic regression models based on age, serum tPSA, %fPSA, and PSAV categorized by two groups. The probability of detection of prostate cancer with Gleason score 7 or greater according to risk factors, including initial %fPSA and PSAV, was examined by Kaplan–Meier analysis, and the significance of the differences was analyzed by the log-rank test. All statistical assessments were performed, and the figures were prepared using commercially available software (SPSS Statistics; IBM, Armonk, NY; and Prism; GraphPad Software, San Diego, CA, USA). In all analyses, $p<0.05$ indicated statistical significance.

Results

The results of prostate repeat biopsies after negative initial biopsy in men eligible for this study are shown in Table I. Out of the 178 men who subsequently underwent repeat biopsies, 48 (27.0%) were pathologically diagnosed with prostate cancer during the observation period. In terms of prostate cancer detection, there were no statistically significant differences in age and serum tPSA levels at initial and latest biopsy between patients with prostate cancer and men without prostate cancer. The %fPSA at initial and latest biopsy and the value of change in %fPSA were significantly lower in the patients with prostate cancer than in the men without cancer. PSAV from initial to latest biopsy was significantly higher in patients with prostate cancer than men without cancer. The observation period and the number of prostate biopsies was not statistically significantly different between the two groups.

The clinical characteristics of the patients with prostate cancer detected by repeat biopsies are shown in Table II. Among 48 patients, one (2.1%) had locally advanced cancer, and one (2.1%) had metastatic disease. The pathological examination revealed prostate cancer with Gleason score of 7 or more in 17 patients (35.4%).

Table I. *Clinical characteristics of men who underwent subsequent repeat prostate biopsies after negative results on initial biopsy.*

Variable	Prostate cancer	Nonprostate cancer	*p*-Value
Men (n)	48	130	
Age at initial biopsy (years)	64 (62-66)	63 (61-65)	0.1892
Serum PSA at initial biopsy (ng/ml)	3.25 (2.6-4.2)	3.50 (2.7-4.4)	0.3996
Free PSA at initial biopsy (%)	12.4 (10.0–16.0)	14.3 (11.0-18.0)	0.0459
Serum PSA at latest biopsy (ng/ml)	4.85 (4.4-6.4)	4.55 (3.4–6.0)	0.1844
Free PSA at latest biopsy (%)	10.6 (9.0–13.0)	14.1 (11.0-18.0)	<0.0001
Initial latest biopsy (months)	33.8 (23-44)	35.8 (23–54)	0.4024
PSAV (ng/ml/years)	0.515 (0.23-0.82)	0.297 (0.07-0.68)	0.0172
Free PSAV (ng/ml/year)	0.038 (0.01-0.07)	0.032 (0.00-0.08)	0.7419
Change of % free PSA	−1.61 (−3.9-0.5)	−0.14 (−2.5-1.8)	0.0292
Number of biopsy (n)	2 (2–2)	2 (2–2)	0.5631

Data are median values (interquartile range). Mann–Whitney U-test. PSA, prostate-specific antigen; PSAV, prostate-specific antigen velocity.

Table II. *Clinical characteristics of the patients diagnosed by repeat biopsy.*

Characteristic	No. of patients (%)
Age at diagnosis (years)	
55-64	1 (2.1)
60-64	10 (20.8)
65-69	31 (64.6)
70-75	6 (12.5)
Gleason score	
≤6	29 (60.4)
7	12 (25.0)
8-10	5 (10.4)
Unknown	2 (4.2)
PSA at diagnosis (ng/ml)	
2.1-4.0	11 (22.9)
4.1-7.0	26 (54.2)
7.1-10.0	11 (22.9)
Clinical stage	
T1c N0 M0	36 (75.0)
T2 N0 M0	6 (12.5)
T3b N0 M0	1 (2.1)
T3a N0 M1a	1 (2.1)
Unknown	4 (8.3)

PSA, Prostate-specific antigen; T, tumor; N, node; M, metastasis.

Table III shows the results of univariate and multivariate logistic regression analysis for prostate cancer detection based on age, serum tPSA level, %fPSA, and PSAV from initial to latest biopsy. In the category setting of this study, the majority of participants were within the serum tPSA range of 2.1-4.0 ng/ml at initial biopsy (64.0%) and had a PSAV of ≤0.40 ng/ml/year (56.7%). On univariate and multivariate analysis, %fPSA ≤12 at latest biopsy and PSAV >0.40 were determined to be significant predictors for detecting prostate cancer. Regarding prostate cancer with Gleason score of 7 or more, serum tPSA levels of 2.1-4.0 ng/ml at initial biopsy, %fPSA ≤12 at initial and latest biopsy, and PSAV >0.40 were determined to be significant predictors for detecting these carcinomas on univariate analysis, and %fPSA ≤12 at initial biopsy and PSAV >0.40 were determined to be those on multivariate analysis.

Kaplan–Meier curves of the cumulative probabilities of developing prostate cancer with Gleason score of 7 or more categorized by %fPSA at initial biopsy and PSAV are shown in Figure 1; %fPSA ≤12 and PSAV >0.40 ng/ml/year were each scored as 1 point, and cases were then categorized into three groups: there were 26 (14.8%), 94 (53.4%), and 56 (31.8%) men with 2 points, 1 point, and 0 points, respectively. The probability of developing prostate cancer of Gleason score 7 or more after 5 years (95% confidence interval) were 55.8% (28.5%-83.1%), 14.8% (3.08%-26.5%), and 4.0% (0%-11.7%), in men with 2 points, 1 point, and 0 points, respectively. There were statistically significant differences in the these probabilities between men with 2 points and those with 0 or 1 points on the log-rank test.

Discussion

Several studies, including our previous study, demonstrated that the risk of prostate cancer development significantly increases with higher baseline PSA range (12-15). In men with a serum PSA <1.0 ng/ml, the risk of being diagnosed with cancer in the next 4-7 years after initial screening is very low (below 1.0%), and based on these results, individualized screening intervals for men with baseline serum PSA levels of ≤1.0 ng/ml are recommended in clinical guidelines for prostate cancer (*i.e.* 8 years in the European Association of Urology guidelines, 3 years in the Japanese Urological Association guidelines) (1, 16). In contrast, the optimal protocol for the screening management of men with serum PSA above cut-off levels, especially after negative biopsy results, remains unclear (1, 6). The positive rates in subsequent prostate biopsies after negative initial biopsy results were reported to be 10-47% in a previous study (5), and these high rates indicate that the management of candidates who have a negative result in initial biopsy is a serious concern.

Table III. *Logistic regression analyses for prostate cancer detection according to age, serum total prostate specific antigen (PSA), and %free PSA in men with total PSA level of 2.1-10.0 ng/ml who underwent repeat biopsies.*

		Prostate cancer detection				Cancer of Gleason score ≥7			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	No.	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age at initial biopsy (years)									
≤64	108	1 (Reference)				1 (Reference)			
≥65	70	1.29 (1.15-1.36)	0.463			1.39 (0.51-3.80)	0.520		
PSA at initial biopsy (ng/ml)									
2.1-4.0	114	1 (Reference)				1 (Reference)		1 (Reference)	
4.1-10.0	64	0.66 (0.32-1.35)	0.253			0.21 (0.05-0.97)	0.045	0.23 (0.05-1.10)	0.066
Free PSA at initial biopsy (%)									
>12.0	106	1 (Reference)				1 (Reference)		1 (Reference)	
≤12.0	72	1.71 (0.88-3.33)	0.116			5.66 (1.76-18.2)	0.004	4.64 (1.24-17.4)	0.023
PSA at diagnosis (ng/ml)									
2.1–4.0	59	1 (Reference)				1 (Reference)			
4.1–10.0	119	1.97 (0.92-4.22)	0.081			1.72 (0.54-5.52)	0.363		
Free PSA at diagnosis (%)									
>12.0	94	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
≤12.0	84	3.89 (1.90-7.95)	<0.001	3.58 (1.73-7.41)	0.001	10.3 (2.28-46.6)	0.002	3.93 (0.76-20.3)	0.102
PSAV (ng/ml/years)									
≤0.4	101	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
>0.4	77	2.94 (1.48–5.84)	0.002	2.26 (1.12-4.58)	0.023	3.66 (1.23-10.9)	0.020	3.56 (1.08-11.8)	0.037
Change in % free PSA									
No change, increase	88	1 (Reference)				1 (Reference)			
Decrease	90	1.94 (0.99-3.83)	0.055			1.95 (0.69-5.54)	0.208		

CI, Confidence interval; OR, odds ratio; PSAV, prostate-specific antigen velocity.

To improve the cancer detection rate in repeat biopsies, several markers, including initial serum PSA, PSA kinetics, %fPSA, pathological findings of initial biopsy and prostate volume, have been reported (5, 6), and a nomogram comprising these risk factors may be useful for selecting an indication of repeat biopsy (4, 7, 8). Moreover, multiparametric MRI may potentially have clinical use in aiding the diagnostic pathways of men at risk (17). However, these risk factors and modalities can be obtained on an outpatient clinic basis during follow-up and not during screening follow-up, given the imbalance of cost and clinical benefit. For men with a negative initial biopsy who are followed-up by population screening, simple markers that can be obtained and determined easily and objectively should be used for selecting screened patients who need a repeat biopsy.

In the present study, we retrospectively investigated the detection rate and cancer characteristics of prostate cancer in repeat biopsies using our population-based screening cohort. The Kanazawa population-based screening cohort is now prospectively establishing a database including individual medical information on screening and biopsy results and clinicopathological features of prostate cancer detected during screening. One of the unique characteristics of the Kanazawa population-based screening cohort is a dataset of %fPSA in participants with serum PSA levels of 2.1-10.0 ng/ml, and we previously reported that %fPSA was a strong predictor of future cancer detection and unfavorable cancer features in prostate biopsy in men with tPSA levels of 2.1-10.0 ng/ml during population screening (18). In the present study, we demonstrated that %fPSA and PSAV were independent risk factors for the detection of prostate cancer in repeat biopsies in men with serum tPSA within this range during the population screening follow-up.

PSAV is a useful marker for identifying men at risk of aggressive prostate cancer. However, the usefulness of PSAV alone to predict prostate cancer on repeat biopsies has been reported as being limited (19, 20). The optimal PSAV threshold also remains unclear [0.75 ng/ml/year (19) and 0.48 (5)] because it may depend on the background of the study population, including serum PSA range at initial and repeat biopsies and patient ethnicity. Considering that persistent PSA >10 ng/ml is traditionally agreed upon as a clear indication for repeat biopsy (21), the PSAV threshold should be calculated in the population with serum tPSA ≤10 ng/ml to be useful in the clinical setting. Our present study demonstrated that PSAV >0.4 ng/ml/year was an independent predictor for detecting

prostate cancer in men with serum tPSA of 2.1-10.0 ng/ml, which was lower than those in previous studies. These findings indicate that the PSAV thresholds that were previously associated with cancer detection in repeat biopsies may not be appropriate for use in the Japanese population, with diagnostically gray areas of tPSA levels.

The usefulness of %fPSA in detecting prostate cancer in repeat biopsies is well known, and the thresholds of %fPSA were reported to be 10-30% (21, 22). Our present study showed that %fPSA ≤12 at the latest biopsy was a significant predictor for detecting prostate cancer and high-grade cancer. Interestingly, %fPSA ≤12 at the initial biopsy was an independent risk factor for detecting prostate cancer with Gleason score of 7 or greater. This finding is clinically relevant because men with %fPSA ≤12 should be carefully followed-up after presenting a negative initial biopsy. Cumulative risks for the detection of prostate cancer with Gleason score 7 or more were simply divided by the combinations of values of %fPSA at initial biopsy and PSAV, which were determined as independent predicting factors in our present study (Figure 1). Cumulative risk was very high in the men with low %fPSA at initial biopsy and high PSAV, and in contrast, prostate cancer with Gleason score of 7 or greater was diagnosed in only one of the men with high %fPSA and low PSAV during the observation period. Regarding population screening follow-up, there is a growing awareness of the potential for over-diagnosis and over-treatment of cases of 'insignificant' or 'minimal' prostate cancer, particularly with the use of low cutoff levels of serum tPSA as in our screening system. Although further examination is needed, simple risk stratification combining %fPSA at initial biopsy and PSAV may become a useful method for selecting screened patients who need repeat biopsy.

The present study had several limitations related to the retrospective nature of the analysis in this screening cohort. Firstly, there were possible biases related to the time from initial to latest biopsy because of the irregular intervals of re-screening and the different decisions of urologists. Secondly, repeat prostate biopsy methods, including extended biopsy, were different between the several participating Institutions in the population screening program. Thirdly, noncancer-related PSA increase secondary to inflammation (23) could not be excluded in the present study because PSAV was calculated from two points of serum PSA. Fourthly, we did not account for abnormal pathological findings including high-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation in the initial biopsy, which have been reported as risk factors for cancer on repeat biopsy (6). Further prospective large-scale studies using fixed repeat biopsy intervals are, therefore, needed. However, the present study results show that in simple risk stratification, %fPSA combined with PSAV was an independent risk factor for detecting high-grade prostate cancer in repeat biopsy on a population screening basis. Our present results contribute to the establishment of individualized and natural history-adjusted screening systems for men with serum tPSA of 2.1-10 ng/ml; the %fPSA values on initial biopsy may decide individual intervals to the next PSA test after negative initial biopsy, and PSAV may provide more information for the adequate timing of repeat biopsy.

Conflicts of Interest

There are no conflicts of interest to declare.

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References

1 Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F and Mottet N: European Association of Urology: EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol *65*: 124-137, 2014.

2 O'Dowd GJ, Miller MC, Orozco R and Veltri RW: Analysis of repeated biopsy results within 1 year after a noncancer diagnosis. Urology *55*: 553-559, 2000.

3 Roehl KA, Antenor JAV and Catalona WJ: Serial biopsy results in prostate cancer screening study. J Urol *167*: 2435-2439, 2002

4 Benecchi L, Pieri AM, Melissari M, Potenzoni M and Pastizzaro CD: A novel nomogram to predict the probability of prostate cancer on repeat biopsy. J Urol *180*: 146-149, 2008.

5 Okada K, Okihara K, Kitamura K, Mikami K, Ukimura O, Kawauchi A, Kamoi K, Nakao M and Miki T: Community-based prostate cancer screening in Japan: predicting factors for positive repeat biopsy. Int J Urol *17*: 541-547, 2010.

6 Zayton OM and Jones JS: Prostate cancer detection after a negative prostate biopsy: lessons learnt in the Cleaveland Clinic experience. Int J Urol *18*: 557-568, 2011.

7 Moussa AS, Jones JS, Yu C, Fareed K and Kattan MW: Development and validation of a nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session in the era of extended prostate sampling. BJU Int *106*: 1309-1314, 2010.

8 Sakura M, Kawakami S, Ishioka J, Fujii Y, Yamamoto S, Iwai A, Numao N, Saito K, Koga F, Masuda H, Kumagai J, Yonese J, Fukui I and Kihara K: A novel repeat biopsy nomogram based on three-dimensional extended biopsy. Urology *77*: 915-920, 2010.

9 Kobori Y, Kitagawa Y, Mizokami A, Komatsu K and Namiki M: Free-to-total prostate-specific antigen (PSA) ratio contributes to an increased rate of prostate cancer detection in a Japanese population screened using a PSA level of 2.1-10.0 ng/ml as a criterion. Int J Clin Oncol *13*: 229-232, 2008.

10 Kitagawa Y, Mizokami A, Nakashima K, Koshida K, Shimamura M, Miyazaki K, Koyama N and Namiki M: Clinical outcomes of prostate cancer patients detected by prostate-specific antigen-based population screening in Kanazawa City, Japan. Int J Urol *18*: 592-596, 2011.

11 International Union Against Cancer: Urologic Tumors: Prostate. In: TNM Classification of Malignant Tumours. Fifth Edition. Sobin LH and Wittekind CH (eds.). New York, John Wiley & Sons, pp. 170-173, 1997.

12 Aus G, Damber JE, Khatami A, Lilja H, Stranne J and Hugosson J: Individualized screening interval for prostate cancer based on prostate-specific antigen level: results of a prospective, randomized, population-based study. Arch Intern Med *165*: 1857-1861, 2005.

13 Ito K, Raaijmakers R, Roobol M, Wildhagen M, Yamanaka H and Schröder FH: Prostate carcinoma detection and increased prostate-specific antigen levels after 4 years in Dutch and Japanese males who had no evidence of disease at initial screening. Cancer *103*: 242-250, 2005.

14 Candas B, Labrie F, Gomez JL, Cusan L, Chevrette E, Lévesque J and Brousseau G: Relationship among initial serum prostate-specific antigen, prostate-specific antigen progression and prostate cancer detection at repeat screening visits. J Urol *175*: 510-517, 2006.

15 Sawada K, Kitagawa Y, Ito K, Takeda Y, Mizokami A and Namiki M: Cumulative risk of developing prostate cancer in men with low (≤2.0 ng/ml) prostate-specific antigen levels: A population-based screening cohort study in Japan. Int J Urol *21*: 560-565, 2014.

16 Committee for Establishment of the Guidelines on Screening for Prostate Cancer; Japanese Urological Association: Updated Japanese Urological Association Guidelines on prostate-specific antigen-based screening for prostate cancer in 2010. Int J Urol *17*: 830-838, 2010.

17 Arumainayagam N, Ahmed HU, Moore CM, Freeman A, Allen C, Sohaib SA, Kirkham A, van der Meulen J and Emberton M: Multiparametric MR imaging for detection of clinically significant prostate cancer: a validation cohort study with transperineal template prostate mapping as the reference standard. Radiology *268*: 761-769, 2013.

18 Kitagawa Y, Ueno S, Izumi K, Kadono Y, Konaka H, Mizokami A and Namiki M: Cumulative probability of prostate cancer detection in biopsy according to free/total PSA ratio in men with total PSA levels of 2.1-10.0 ng/ml at population screening. J Cancer Res Clin Oncol *140*: 53-59, 2014.

19 Keetch DW, McMurtry JM, Smith DS, Andriole GL and Catalona WJ: Prostate-specific antigen density *versus* prostate-specific antigen slope as predictors of prostate cancer in men with initially negative prostate biopsies. J Urol *156*: 428-431, 1996.

20 Vickers AJ, Wolters T, Savage CJ, Cronin AM, O'Brien MF, Roobol MJ, Aus G and Scardino PT: Prostate-specific antigen velocity does not aid prostate cancer detection in men with prior negative biopsy. J Urol *184*: 907-912, 2010.

21 Djavan B, Remzi M, Schuluman CC, Merberger M and Zlotta AR: Repeat prostate biopsy: Who, how and when? A review. Eur Urol *42*: 93-103, 2002

22 Morgan TO, McLeod DG, Leifer ES, Murphy GP and Moul JW: Prospective use of free prostate-specific antigen to avoid repeat prostate biopsies in men with elevated total prostate-specific antigen. Urology *48*: 76-80, 1996.

23 Ito K, Yamamoto T, Ohi M, Takechi H, Kurokawa K, Suzuki K and Yamanaka H: Natural history of PSA increase with and without prostate cancer. Urology *62*: 64-69, 2003.

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