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Original Article: Clinical Investigation

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

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Abbreviations & Acronyms
DRE = digital rectal examination
PSA = prostate-specific antigen
TRUS = transrectal ultrasonography

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Objectives: To investigate the natural history of men with low levels of baseline prostate-specific antigen in terms of risk of increased prostate-specific antigen, developing prostate cancer and also the likelihood of detecting clinically insignificant cancer in population-based screening.

Methods: A total of 10 653 men aged between 55 and 68 years with baseline prostate-specific antigen levels of 2.0 ng/mL or lower screened annually were enrolled. The cumulative risks of increased prostate-specific antigen and developing cancer were investigated. The relationships of baseline prostate-specific antigen with clinicopathological features of screening-detected cancer were also investigated.

Results: A total of 1405 men (13.2%) showed serum prostate-specific antigen above 2.0 ng/mL and 68 (0.6%) were diagnosed with prostate cancer during the observation period. Cumulative probabilities of increased prostate-specific antigen above 2.0 ng/mL over 10 years were 7.7%, 18.3%, 57.3%, and 88.7% in men with baseline prostate-specific antigen levels of 0.0–0.5, 0.6–1.0, 1.1–1.5, and 1.6–2.0 ng/mL, respectively. The cumulative probabilities of developing prostate cancer at 4 years in men with baseline prostate-specific antigen of 0.0–1.0 and 1.1–2.0 ng/mL were 0.05% and 1.10%, respectively. Patients with unfavorable clinicopathological features were diagnosed at 3 years, and at 1 year after the initial screening visit in men with baseline prostate-specific antigen levels of 0.0–1.0 and 1.1–2.0 ng/mL, respectively.

Conclusions: The cumulative probabilities of increased prostate-specific antigen and developing prostate cancer significantly increase with higher baseline prostate-specific antigen ranges. Our database could contribute to the establishment of a natural history-adjusted screening system in the future.

Key words: prostate cancer, prostate-specific antigen, risk factor, screening.

Introduction

PSA-based screening was found to benefit survival in males aged 50–69 years in the European Randomized Study of Screening for Prostate Cancer[1] and the Göteborg prospective randomized study.[2] These studies further showed that one male per 1055 screened, primarily at 4-year intervals,[1] and one male per 293 screened at 2-year intervals,[2] would not suffer prostate cancer-related death over a decade. These benefits on mortality reduction could be much greater over a lifetime. However, it is necessary to establish an optimal screening system that maximizes the benefits of PSA-based screening in terms of mortality reduction and cost-effectiveness, while minimizing drawbacks of screening in terms of likelihood of overdetection.

From this point of view, setting individualized screening, including screening interval, cut-offs for biopsy indication and upper limit of age for screening, might save on the costs of screening, and reduce the likelihood of overdetection and false positive PSA test results, while maintaining the benefit of mortality reduction. The Kanazawa population-based screening cohort is a database linking individual screening results and medical information of screening-detected cancer patients. Our database might contribute to answering the aforementioned clinical questions regarding how to establish individualized screening systems in the future.

In the present study, the natural history of participants in the baseline PSA range of 0.0–2.0 ng/mL during follow up for up to 12 years was investigated in terms of risk of increased PSA

Table 1 Clinical characteristics of participants with PSA levels ≤2.0 ng/mL at the initial screening

Variables	All	Age range (years)		
		55–59	60–64	65–68
No. men	10 653	3195	4736	2722
Initial PSA (ng/mL)				
Mean	0.89	0.84	0.90	0.93
Median	0.8	0.8	0.8	0.8
Initial PSA range (ng/mL)				
0.0–0.5	2 804 (26.3)	911 (28.5)	1246 (26.3)	647 (23.8)
0.6–1.0	4 432 (41.6)	1397 (43.7)	1935 (40.9)	1100 (40.4)
1.1–1.5	2 246 (21.1)	612 (19.2)	1021 (21.6)	613 (22.5)
1.6–2.0	1 171 (11.0)	275 (8.6)	534 (11.3)	362 (13.3)
No. screenings				
Mean	4.26	5.06	4.55	2.79
Median	4	4	4	3
Range	2–12	2–12	2–10	2–5
Initial to last screenings				
Mean (day)	1 531.5	2073.0	1624.3	734.3
Median (day)	1 412	2131	1686	724
Range (day)	189–4164	189–4164	212–3418	195–1627
PSA increase				
Above 2.0 ng/mL	1 405 (13.2)	453 (14.2)	710 (15.0)	242 (8.9)
Above 3.0 ng/mL	468 (4.4)	169 (5.3)	251 (5.3)	48 (1.8)
Above 4.0 ng/mL	215 (2.0)	82 (2.6)	110 (2.3)	23 (0.8)
No. prostate biopsy	309 (2.9)	112 (3.5)	160 (3.4)	37 (1.4)
No. prostate cancer	68 (0.6)	21 (0.7)	39 (0.8)	8 (0.3)

above the cut-offs of 2.0, 3.0 and 4.0 ng/mL, developing clinically detectable cancer and also the likelihood of detecting clinically insignificant cancer in the Kanazawa screening cohort, including over 10 000 men screened annually and aged at baseline between 55 and 68 years.

Methods

Since 2000, PSA-based screening has been provided for men aged between 55 and 69 years in Kanazawa city, Japan.[3,4] All participants had serum total PSA levels measured using a Tosoh II PA kit (Tosoh, Tokyo, Japan) as a primary screening modality. Participants with serum PSA of 2.0 ng/mL or lower did not proceed to secondary screening and were recommend to be screened annually. In participants with PSA between 2.1 and 10.0 ng/mL, serum free PSA levels were checked using an Immulyze Free PSA kit (Nippon DPC, Chiba, Japan).

From 2000 to 2002, participants with serum PSA levels above 2.0 ng/mL were recommended to proceed to secondary screening by urologists. After 2003, participants with serum PSA above 10.0 ng/mL and those with serum free/total PSA ratio of 0.22 or lower in the PSA range of 2.1–10.0 ng/mL were recommended to proceed to secondary screening.[3,4]

PSA levels were measured again in men who proceeded to secondary screening, and DRE and TRUS were carried out by urologists at the urological departments. Systematic TRUS-guided prostate biopsy was recommended in men with any abnormal findings on rechecked PSA, DRE or TRUS. If individuals did not agree to undergo prostate biopsy or were not recommended to undergo biopsy at the secondary screening, they were followed up by an annual PSA test at a subsequent population-based screening.

In patients diagnosed with prostate cancer, 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,[5] based on the results of DRE, TRUS computed tomography, magnetic resonance imaging and bone scan at each urological department. The aforementioned medical information, including PSA levels at screening, biopsy results and clinicopathological findings, were reported to the office of the Kanazawa Medical Association.

In the Kanazawa population-based cohort, 19 640 men participated in the screening program during the 12 years from 2000 to 2011, and 16 393 (83.5%) had serum PSA levels of 2.0 ng/mL or lower at the initial screening. Of 16 393 men, 10 653 (65.0%) participants who were aged at baseline between 55 and 68 years old and were actually screened annually at least twice during the observation periods were enrolled into the present study. We investigated cumulative risk of increased PSA above 2.0, 3.0, and 4.0 ng/mL and developing prostate cancer. We also investigated clinicopathological features of screening-detected cancer stratified into favorable or unfavorable cancer according to the definition of active surveillance studies.[6,7] We handled prostate cancer with a clinical stage of T1cN0M0, PSA below 10 ng/mL, Gleason score of 6 or less and one or two positive cores within 6–12 systemic biopsy cores taken as favorable cancer.

In the present retrospective study, the principles of the Declaration of Helsinki were followed. Probabilities of developing prostate cancer and PSA increase above the cut-offs were analyzed by Kaplan–Meier analysis. The significance of differences was analyzed by the log–rank test. In analyses of

Table 2 Probability of increased PSA above cut-off and prostate cancer detection according to baseline PSA level during the observation period

Variables	Baseline PSA range (ng/mL)			
	0.0–0.5	0.6–1.0	1.1–1.5	1.6–2.0
No. participants	2804	4432	2246	1171
No. men with increased PSA				
Above 2.0 ng/mL	59 (2.1%)	261 (5.9%)	490 (21.8%)	595 (50.8%)
Above 3.0 ng/mL	28 (1.0%)	102 (2.3%)	165 (7.3%)	173 (14.8%)
Above 4.0 ng/mL	13 (0.5%)	48 (1.1)	71 (3.2)	83 (7.1)
No. men undergoing prostate biopsy	9 (0.3%)	37 (0.8%)	118 (5.3%)	145 (12.4%)
No. men diagnosed with prostate cancer	0	6 (0.1%)	30 (1.3%)	32 (2.7%)

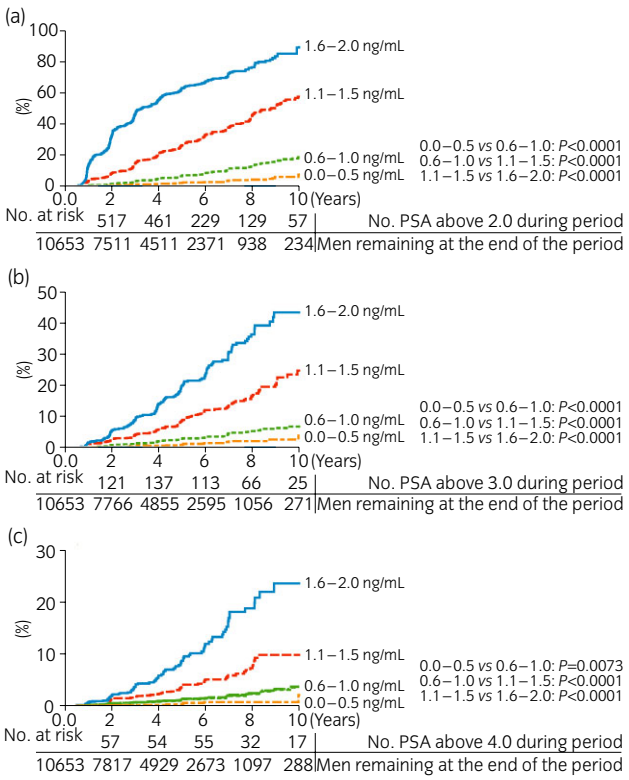

Fig. 1 Cumulative probabilities of first increased PSA above (a) 2.0 ng/mL, (b) 3.0 ng/mL and (c) 4.0 ng/mL during follow up in men with baseline PSA of 2.0 ng/mL or less.

probabilities, men without evidence of cancer and also PSA increase above 2.0 ng/mL were censored at the time of last screening. All statistical analyses were carried out using SPSS Statistics (IBM, Armonk, NY, USA) and Prism (GraphPad Software, San Diego, CA, USA). In all analyses, $P < 0.05$ was taken to show statistical significance.

Results

The clinical characteristics of 10 653 eligible men included in the present study are shown in Table 1. Of the 10 653 men with baseline PSA levels of 0.0–2.0 ng/mL at the initial screen, 1405 men (13.2%) showed elevated serum PSA above 2.0 ng/mL, and 68 (0.6%) were diagnosed with prostate cancer during the observation period. The median duration from initial to last screening was 3.9 years, and the median screening number was four times.

The numbers and percentages of men with increased PSA above 2.0, 3.0 and 4.0 ng/mL, men undergoing biopsy, and patients diagnosed with prostate cancer, stratified by baseline PSA ranges, are shown in Table 2. No prostate cancer patients were detected among men with a baseline PSA of 0.0–0.5 ng/mL during the observation period. Cumulative probabilities of increased PSA above 2.0, 3.0 and 4.0 ng/mL stratified by baseline PSA range were estimated by Kaplan–Meyer analysis (Fig. 1). The probabilities of increased PSA above 2.0 ng/mL during 10 years were 7.7%, 18.3%, 57.3%, and 88.7% in men with baseline serum PSA levels of 0.0–0.5, 0.6–1.0, 1.1–1.5, and 1.6–2.0 ng/mL, respectively (Fig. 1a). The probabilities of increased PSA above 3.0 ng/mL during 10 years were 4.1%, 6.7%, 24.6%, and 43.2% in men with baseline serum PSA levels of 0.0–0.5, 0.6–1.0, 1.1–1.5, and 1.6–2.0 ng/mL, respectively (Fig. 1b). The probabilities of increased serum PSA above 4.0 ng/mL during 10 years were 2.2%, 3.6%, 9.8%, and 23.6% in men with baseline serum PSA levels of 0.0–0.5, 0.6–1.0, 1.1–1.5, and 1.6–2.0 ng/mL, respectively (Fig. 1c). There were significant differences in the probabilities of increased PSA above 2.0, 3.0 and 4.0 ng/mL when comparing men with any two different baseline PSA ranges.

The cumulative probabilities of cancer detection stratified by PSA and age ranges at baseline are shown in Figure 2a–c. The cumulative probability of cancer detection in men with baseline PSA levels between 0.0 and 0.5 ng/mL was 0.0% in all age ranges. The cumulative probabilities of developing prostate cancer increased significantly with higher baseline PSA ranges in all participants (Fig. 2a). We examined the likelihood of developing cancer stratified by age range at baseline, and found that the cumulative probability of cancer detection in men with baseline PSA levels of 1.1–2.0 ng/mL was significantly higher than that in men with baseline PSA levels of 0.6–1.0 ng/mL in both the age ranges of 55–59 years and 60–64 years. However, the difference in cumulative probability of cancer detection between men with baseline PSA levels of 1.1–1.5 ng/mL and 1.6–2.0 ng/mL was not significant in both the age ranges of 55–59 years (Fig. 2b) and 60–64 years (Fig. 2c).

Table 3 shows the longitudinal changes in cumulative probability of cancer detection stratified by age and PSA level at baseline. In men with baseline PSA levels of 0.0–1.0 ng/mL, the first prostate cancer cases were detected at 5 years, 4 years and 3 years after the initial screening visit in the age at baseline of 55–59 years, 60–64 years and 65–68 years, respectively. In men with baseline PSA levels of 1.1–2.0 ng/mL, the first prostate cancer cases were detected at 2 years and 1 year after the

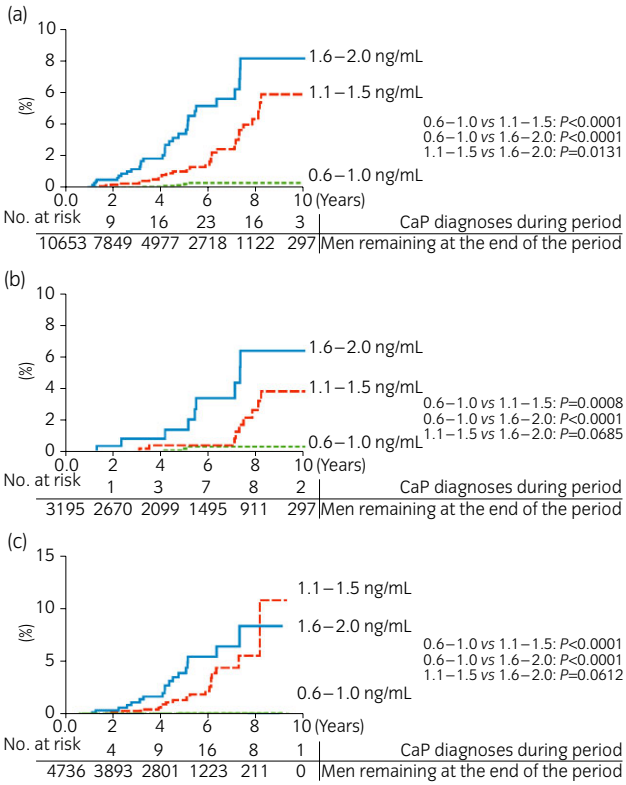

Fig. 2 Cumulative probabilities of developing prostate cancer during follow up in (a) all participants, (b) men aged 55–59 years and (c) 60–64 years with baseline PSA of 2.0 ng/mL or lower.

initial screening visit in the age at baseline of 55–64 years and 65–68 years, respectively.

The clinical characteristics of prostate cancer patients detected in the present study are shown in Table 4. Among 68 patients, one (1.5%) had locally advanced cancer and one (1.5%) had metastatic disease. A total of 17 (25.0%) patients had favorable clinicopathological features that made them suitable for active surveillance. Table 5 shows the correlation of baseline PSA levels and the number of years elapsed after initial screening visit with clinicopathological characteristics of prostate cancer stratified by suitability for active surveillance. Among six patients diagnosed with prostate cancer at subsequent screening in the baseline PSA range of 0.0 to 1.0 ng/mL, four patients were able to obtain clinicopathological features to be stratified by suitability of active surveillance. Of these four patients, one (25.0%) patient in whom prostate cancer was detected at 5 years after the initial screening visit had favorable clinicopathological features that were suitable for active surveillance. In the baseline PSA range of 1.1–2.0 ng/mL, nine patients were diagnosed with prostate cancer within 2 years after initial screening. Of these nine patients, four (44.4%) had prostate cancer with favorable clinicopathological features.

Discussion

It is very important to determine the natural history of prostate cancer and to explore risk factors for the development of clinically significant cancer, to establish an optimal early detection program and treatment strategy. PSA-based screening was found to benefit survival in previous reliable randomized studies, but it is necessary to establish an optimal screening system that maximizes mortality reduction and cost-effectiveness while minimizing the drawbacks of screening, such as overdetection, subsequent overtreatment and adverse effects on quality of life.

The Kanazawa population-based screening cohort is prospectively establishing a database including individual medical information on screening results, subsequent biopsy results and clinicopathological features of screening-detected cancer. In the present study using this screening cohort, we tried to investigate the natural history of PSA in men with low PSA levels at initial screening.

Several studies showed cumulative probabilities of increased PSA above the cut-offs and development of prostate cancer in subsequent screening in men with baseline serum PSA below the cut-offs.[8–12] However, the participants enrolled into these previous studies did not undergo annual screening. In contrast, the participants in the present study were screened annually during the observation period, and the number of participants was larger than in previous series.[9–11] The present study showed a natural history of participants in the baseline PSA range of 0.0–2.0 ng/mL over observation periods up to 12 years. The longitudinal risk of increased PSA above 3.0 and 4.0 ng/mL might have been underestimated in the present study, because men with PSA above 2.0 ng/mL were recommended to undergo secondary screening and subsequent prostate biopsy, and some of these men were eliminated from the longitudinal screening database if they were diagnosed with prostate cancer. The longitudinal risk of increased PSA above 2.0 ng/mL could be the first reliable reference data in the field of screening for prostate cancer.

With regard to the setting of PSA cut-offs, some previous studies showed the importance of serum PSA level of 2.0 ng/mL as the cut-off for biopsy indication from the viewpoint of cancer detection. Krumholtz *et al*. showed that the detection rate of clinically important prostate cancer among men with a serum PSA level of 2.6–4.0 ng/mL was the same as that among men with serum PSA values greater than 4.0 ng/mL.[13] Thompson *et al*. showed that the rate of prostate cancer detection was similar among men with serum PSA levels of 2.1–3.0 ng/mL and those with levels of 3.1–4.0 ng/mL.[14] The present study provided important data on the risk of developing cancer, and also the likelihood of detecting clinically insignificant cancer in the screening cohort with the PSA cut-off for biopsy set to 2.1 ng/mL.

In the present study, the cumulative probability of cancer detection in men with baseline PSA of 1.1–2.0 ng/mL was significantly higher than in those with baseline PSA of 0.0–1.0 ng/mL. The cumulative probabilities of developing cancer at 4 years in the men with baseline PSA of 1.1–2.0 ng/mL were 0.588%, 1.120%, and 2.719% in those with age at baseline of 55–59 years, 60–64 years, and 65–68 years, respectively. The cumulative risk of developing cancer might be underestimated, because this screening cohort recommended a PSA cut-off for biopsy of 2.1 ng/mL, but this was not severely restricted by the protocol and not all men with PSA above 2.0 ng/mL underwent prostate biopsy. Although it would be difficult to carry out a head-to-head comparison on the cumulative probabilities of

Table 3 Longitudinal changes in the cumulative probability of prostate cancer detection stratified by age and PSA level at baseline

PSA and age at baseline	No. men	Cumulative percentages of prostate cancer detection (95% CI) at specified elapsed years after initial screening					
		1 Year	2 Years	3 Years	4 Years	5 Years	8 Years
0.0–1.0 ng/mL							
All	7236	0	0	0.020 (0–0.06)	0.045 (0–0.11)	0.145 (0.02–0.27)	0.186 (0.03–0.34)
55–59 years	2308	0	0	0	0	0.143 (0–0.20)	0.224 (0–0.48)
60–64 years	3181	0	0	0	0.045 (0–0.14)	0.108 (0–0.26)	0.108 (0–0.26)
65–68 years	1747	0	0	0.146 (0–0.43)	0.146 (0–0.43)	NA	NA
1.1–2.0 ng/mL							
All	3417	0.031 (0–0.09)	0.313 (0.11–0.52)	0.580 (0.29–0.88)	1.098 (0.65–1.55)	1.826 (1.19–2.46)	5.633 (3.97–7.30)
55–59 years	887	0	0.126 (0–0.37)	0.268 (0–0.37)	0.588 (0.01–1.17)	0.765 (0.09–1.44)	3.835 (1.91–5.74)
60–64 years	1555	0	0.292 (0.01–0.57)	0.624 (0.19–1.06)	1.120 (0.51–1.73)	2.246 (1.30–3.20)	6.598 (3.86–9.34)
65–68 years	975	0.113 (0–0.33)	0.553 (0.01–1.10)	0.829 (0.06–1.60)	2.719 (0.02–5.42)	NA	NA

Table 4 Clinical characteristics of patients diagnosed with prostate cancer within subsequent screening in men with baseline PSA between 0.0 and 2.0 ng/mL

Characteristics	No. patients (%)
Age at diagnosis (years)	
55–59	3 (4.4)
60–64	20 (29.4)
65–69	45 (66.2)
Gleason score	
≤6	34 (50.0)
7	20 (29.4)
8–10	10 (14.7)
Unknown	4 (5.9)
PSA at diagnosis (ng/mL)	
2.1–4.0	48 (70.6)
4.1–9.9	18 (26.5)
≥10.0	2 (2.9)
Clinical stage	
T1c N0 M0	45 (66.2)
T2 N0 M0	18 (26.5)
T3a N0 M0	1 (1.5)
T3a N0 M1b	1 (1.5)
Unknown	3 (4.4)
No. positive biopsy cores	
≤2	37 (54.4)
≥3	21 (30.9)
Unknown	10 (14.7)
Suitability for active surveillance	
Yes (PSA <10.0, T1c, GS ≤6 and positive biopsy cores ≤2)	17 (25.0)
No (PSA ≥10.0 or ≥ T2 or GS ≥7 or positive biopsy cores ≥3)	43 (63.2)
Unknown	8 (11.8)

developing cancer among different study cohorts because there could be differences in the underlying background in the setting of PSA cut-off, biopsy compliance and biopsy methods, the age-stratified probabilities shown in the present study were similar to those in each corresponding age group in a previous Canadian study (0.64% in men aged 55 years and PSA of 1.5 ng/mL at baseline to 2.43% in men aged 70 years and PSA of 2.0 ng/mL at baseline).[11] Furthermore, a previous head-to-head comparative study showed that the cumulative probability of cancer detection in Japanese men aged 55–74 years with baseline serum PSA of 1.0–1.9 ng/mL at 4 years was 1.3% (95% CI 0.4–2.3%), and the results were not significantly different from those in Dutch men.[10] They also showed that Japanese and Dutch men had the same risks of increased PSA of 4.0 ng/mL or greater after controlling for age and baseline PSA level.[10] The cumulative probability of freedom from PSA increases to levels >4.0 ng/mL after 4 years of observation were also almost the same in the USA black and USA white populations, if baseline PSA levels fell within the same range.[15] Therefore, there might be no ethnic differences in the likelihood of developing prostate cancer in men with the same baseline PSA level and age. These studies support the hypothesis that baseline PSA could be a key issue for establishing an internationally standardized and optimal screening system regardless of race.

In contrast, there is a growing awareness of the potential for overdiagnosis and overtreatment for "insignificant" cancer detected at PSA-based screening, especially using low serum PSA cut-off levels. Therefore, it is also important to clarify clinicopathological features of prostate cancer detected within the screening system. In the present study, there were few patients in advanced stages of prostate cancer, including clinical stage T3 or higher (2.9%), and serum PSA at diagnosis of 10.0 ng/mL or greater (2.9%). In contrast, 63.2% of the patients had unfavorable clinicopathological features that referred excluding criteria for active surveillance studies.[6,7] A previous study using an accelerated failure time model suggested that men with serum PSA between 1.0 and 1.5 ng/mL should be screened every second year, and men with PSA 1.5 ng/mL or greater should be screened every year.[11] The Japanese Urological Association guidelines for PSA-based screening proposed a baseline PSA-adjusted screening interval, which was set every 3 years and annually in men with baseline PSA of 0.0–1.0 ng/mL and 1.1–2.0 ng/mL, respectively.[16] In the present study, all cancer cases with unfavorable clinicopathological features were diagnosed at least 3 years after the initial screening visit in men with baseline PSA levels of 0.0–1.0 ng/mL. In contrast, there was a risk of developing cancer with unfavorable features within 1 year after the initial screening visit in men with baseline PSA of 1.1–2.0 ng/mL. Furthermore, prostate cancer cases with unfavorable clinicopathological features were detected every year, including one case with metastatic lesions diagnosed at 5 years after the initial

Table 5 Correlation of baseline PSA levels and number of elapsed years after initial screening with clinicopathological characteristics of prostate cancer stratified by suitability for active surveillance

Baseline PSA and cancer characteristics	No. patients detected at each year after initial screening visit						
	1 Years	2 Years	3 Years	4 Years	5 Years	8 Years	10 Years
Baseline PSA of 0.0–1.0 ng/mL							
Patient suitable for AS criteria (PSA <10.0, T1c, GS ≤6 and positive cores ≤2)					1		
Patients unfit for AS criteria (PSA ≥10.0 or ≥ T2 or GS ≥7 or positive cores ≥3)			1	1	1		
Baseline PSA of 1.1–2.0 ng/mL							
Patient suitable for AS criteria (PSA <10.0, T1c, GS ≤6 and positive cores ≤2)		4	1	3	2	6	
Patients unfit for AS criteria (PSA ≥10.0 or ≥ T2 or GS ≥7 or positive cores ≥3)	1	4	5	4	7	17	2
Patients with metastatic disease					(1)		

screening visit in this baseline PSA range. Although the number of cancer cases detected was small, our results support the recommendation for screening interval proposed by the Japanese guidelines.[16]

The primary goal of PSA-based population screening is to detect prostate cancer before cancer cells spread to the adjacent organs, lymph nodes or distant organs to save lives and to maintain quality of life by appropriate treatment strategies. Therefore, setting natural history-adjusted rescreening intervals should be carefully considered. We could provide a clue for establishing an optimal screening system by the present study.

Conflict of interest

None declared.

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