

Prostate cancer detection by prostate-specific antigen-based screening in the Japanese Hiroshima area shows early stage, low-grade, and low rate of cancer-specific death compared with clinical detection

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Abstract

Introduction: We investigate the effectiveness of prostate-specific antigen (PSA) screening for prostate cancer. We compare the characteristics of 2 sets of patients: (1) those in whom prostate cancer was detected via PSA screening (the PS group) and (2) those in whom prostate cancer was detected at the outpatient office (the non-PS group).

Methods: Between 2002 and 2010, prostate cancer was detected in 315 patients by PSA screening. Their age, initial PSA level, pathological findings in biopsy specimens, clinical stage, and prognosis were compared with those of 497 prostate cancer patients diagnosed at the outpatient office of the Department of Urology, Hiroshima University, in the same period.

Results: The rates of patients with initial PSA higher than 50 ng/mL, with a Gleason score of 8 or higher, and with clinical stage D were significantly lower in the PS group than those in the non-PS group. The 5-year overall survival and cancer-specific survival in the PS group was 91.3% and 98.2%, respectively; these results were significantly better than those in the non-PS group (86.4%, $p = 0.0178$, and 94.9%, $p = 0.0112$, respectively). A Cox hazard analysis showed that PSA screening was an independent predictive factor for cancer-specific survival.

Conclusions: Although our study is limited by its retrospective nature and small size, the present data indicate that prostate cancer detected in the PS group showed earlier stage, lower grade, and better prognosis than in the non-PS group.

Introduction

In the United States, prostate cancer has the highest incidence of all malignant tumours and the second highest mortality rate.¹ Prostate-specific antigen (PSA)-based screening is widely used to prevent death due to prostate cancer. In men over 50, 75% of them have had their PSA levels measured

at least once and half of them have their levels measured annually.² While both the incidence and mortality rate of prostate cancer in Japan continue to rise, its mortality rate in the United States has significantly decreased due to high rates of PSA screening.³ Although the Japanese Urological Association PSA screening guidelines in 2008 recommend screening in men aged 50 and over, the exposure rate of PSA screening in Japan is still much lower than in the United States.³ To determine whether PSA screening decreases prostate cancer death in Japan, it is essential to demonstrate that PSA screening can improve the chance of survival of prostate cancer patients. Therefore, we investigated whether PSA screening alone (without clinical symptoms) can decrease the mortality rate in Japan. To do this, we compared the outcomes of patients who underwent PSA screening with those of the outpatients.

Methods

Between 2002 and 2010, prostate cancer screening by PSA measurements was performed for men 50 and over in the northern area of Hiroshima Prefecture, Japan. In all screenings, serum PSA levels were measured using the E-test Tosoh II PA assay (Tosoh, Tokyo, Japan). Patients who had abnormal PSA levels were recommended to visit urologists and to undergo further examinations, such as a digital rectal examination (DRE) or a transrectal ultrasound (TRUS). TRUS-guided systematic 10-cores prostate needle biopsies were performed via the transrectal approach if necessary.

The thresholds of the serum PSA levels were set according to previously reported age-specific reference ranges of PSA.⁴ These were 3.0 ng/mL for men between 50-64, 3.5 ng/mL for men between 65-69, and 4.0 ng/mL for men 70 and over.

For this 9-year study period, 334 cases of prostate cancer were detected by PSA screening in Hiroshima Prefecture in Japan and designated as the "PS group," and in the same

period, 500 outpatients were diagnosed with prostate cancer in Hiroshima University Hospital and were designated as the “non-PS group.” No patient was counted in both groups. We excluded 19 patients in the PS group and 3 in the non-PS group due to a lack of information. Ultimately, 315 cases in the PS group and 497 cases in the non-PS group were included in this study. In the non-PS group, 304 cases (61.2%) had symptomatic diseases at their first outpatient office visit. The mean and median follow-up times of both groups were 47.0 and 42.6 months, respectively.

Age, initial PSA level, pathological diagnosis at biopsy, clinical stage, and prognosis were compared between the PS and the non-PS groups.

Statistical analysis

Overall survival (OS), cancer-specific survival (CSS), and biochemical relapse-free survival (bRFS) were determined by the Kaplan-Meier method and analyzed by log-rank testing. Predictive factors for CSS were analyzed using a Cox hazard analysis. Each parameter in the PS and non-PS groups was compared using the Mann-Whitney U-test and chi-squared test. All statistical analyses were conducted using a StatView 5.0 software package (SAS Institute, Cary, NC). A *p* value of less than 0.05 was considered statistically significant.

Results

Patient demographics

The average age of the PS group was 74.3 years old, significantly older than that of the non-PS group (71.0) ($p < 0.0001$) (Table 1). The number of patients over 80 in the PS group was significantly higher than those in the non-PS group ($p < 0.0001$). Although there was no significant difference in the initial PSA (iPSA) between the PS group (1.13-18740 (median: 11.0) ng/mL) and the non-PS group (2.3-923.3 (median: 9.5) ng/mL), the rate of patients whose iPSA was higher than 50 ng/mL was significantly lower in the PS group. The distribution of Gleason scores at biopsy was significantly different. The rate of patients with 6 or lower was significantly higher in the PS group; in addition, the rate of patients with 8 or higher was significantly lower in the PS group. The rate of patients with clinical stage D in the PS group was significantly lower than in the non-PS group.

In patients with stage B, while the percentage of radiation therapy as an initial treatment in the PS group was significantly lower, the percentage of androgen deprivation therapy in the PS group was significantly higher than in the non-PS group (Table 2). This distribution was reflected in all patients. In contrast, in patients with stage C, while the percentage of radiation therapy as an initial treatment in the PS group was significantly higher, the percentage of androgen

Table 1. Demographics of PS group and non-PS group

	PS group (%) (n=315)	Non-PS group (%) (n=497)	<i>p</i> value
Age			
≥80	70 (22.2)	47 (9.5)	<0.0001
70-79	151 (48.0)	249 (50.1)	0.5478
60-69	79 (25.1)	183 (36.8)	0.0005
≤59	15 (4.8)	18 (3.6)	0.4227
Initial PSA (ng/mL)			
≥50.1	24 (7.6)	79 (15.9)	0.0006
20.1-50	48 (15.2)	60 (12.1)	0.1955
10.1-20	72 (22.9)	132 (26.6)	0.2359
4.1-10	150 (47.6)	209 (42.1)	0.1196
≤4	21 (6.7)	17 (3.4)	0.0328
Gleason score			
≥8	66 (21.0)	174 (35.0)	<0.0001
7	145 (46.0)	207 (41.6)	0.2195
≤6	104 (33.0)	116 (23.3)	0.0025
Clinical stage			
B	262 (83.2)	393 (79.0)	0.1494
C	44 (14.0)	42 (8.5)	0.0128
D	9 (2.8)	62 (12.5)	<0.0001

PSA: prostate-specific antigen; PS group: Patients with prostate cancer detected by PSA-based screening in Hiroshima Prefecture. Non-PS group: Patients with prostate cancer diagnosed at the outpatient office at the Hiroshima University Hospital.

Table 2. Distribution of initial treatments in every stage

	PS group	Non-PS group	<i>p</i> value
Stage B	262	393	
RP	98 (37.4)	143 (36.4)	0.7913
RT	21 (8.0)	164 (41.7)	<0.0001
ADT	142 (54.2)	79 (20.1)	<0.0001
AS	1 (0.4)	7 (1.8)	0.1102
Stage C	44	42	
RP	3 (6.8)	3 (7.1)	0.9529
RT	32 (72.7)	18 (42.9)	0.0050
ADT	9 (20.5)	21 (50.0)	0.0041
Stage D	9	62	
RP	0 (0.0)	1 (1.6)	0.7012
RT	0 (0.0)	0 (0.0)	
ADT	9 (100.0)	61 (98.4)	0.7012
Total	315	497	
RP	101 (32.1)	147 (29.6)	0.4536
RT	53 (16.8)	185 (37.2)	<0.0001
ADT	160 (50.8)	158 (31.8)	<0.0001
AS	1 (0.3)	7 (1.4)	0.1251

PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiation therapy; ADT: androgen deprivation therapy; AS: active surveillance; PS group: Patients with prostate cancer detected by PSA-based screening in Hiroshima Prefecture. Non-PS group: Patients with prostate cancer diagnosed at the outpatient office at the Hiroshima University Hospital.

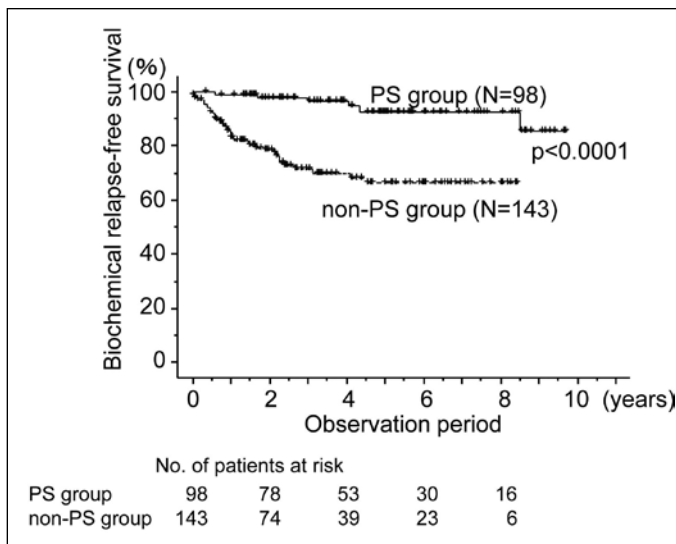


Fig. 1. Biochemical-relapse free survival in patients who underwent radical prostatectomy due to stage B prostate cancer. PSA: prostate-specific antigen; PS group: Patients with prostate cancer detected by PSA-based screening in Hiroshima Prefecture. Non-PS group: Patients with prostate cancer diagnosed by outpatient office in Hiroshima University Hospital. The threshold of PSA level for biochemical recurrence after surgery was defined at 0.2 ng/mL or higher.

deprivation therapy in the PS group was significantly lower than in the non-PS group.

We tallied patients diagnosed as clinical stage B as per the D'Amico risk classification (Table 3). Among these patients, 98 cases in the PS group and 141 cases in the non-PS group underwent radical prostatectomy. Among these patients, the rate of low-risk patients was significantly higher and that of high-risk patients was significantly lower in the PS group compared to the non-PS group. Furthermore, the 5-year bRFS rate was 91.7% in the PS group, significantly better than in the non-PS group (66.1%, $p < 0.0001$) (Fig. 1).

OS and CSS in the PS group and the non-PS group were determined by the Kaplan-Meier method (Fig. 2). There was no significant difference between the 5-year CSS of the PS group and that of the non-PS group in each clinical stage (98.9% and 98.9%, $p = 0.7613$, in stage B; 96.2% and 100%, $p = 0.9944$, in stage C; and 83.3% and 59.8%, in stage D, respectively), nor was there any significant difference between the 5-year OS of the PS group and the non-PS group in each clinical stage (91.3% and 92.1%,

Table 3. D'Amico risk classification in patients with clinical stage B in every treatment option

	PS group	Non-PS group	p value
RP	98	141	
High (%)	13 (13.3)	49 (34.8)	0.0002
Intermediate (%)	53 (54.1)	69 (48.9)	0.4338
Low (%)	32 (32.7)	23 (16.3)	0.0026
RT	21	164	
High (%)	8 (38.1)	44 (26.8)	0.2796
Intermediate (%)	10 (47.6)	75 (45.7)	0.7022
Low (%)	3 (14.3)	45 (27.4)	0.1954
ADT	142	79	
High (%)	46 (32.4)	31 (39.2)	0.3060
Intermediate (%)	67 (47.2)	43 (54.4)	0.8669
Low (%)	29 (20.4)	5 (6.4)	0.0054
AS	1	7	
High (%)	0 (0.0)	0 (0.0)	-
Intermediate (%)	0 (0.0)	1 (14.3)	0.6862
Low (%)	1 (100.0)	6 (85.7)	0.6862
Total	262	391	
High (%)	67 (25.6)	124 (31.7)	0.0909
Intermediate (%)	130 (49.6)	188 (48.1)	0.7002
Low (%)	65 (24.8)	79 (20.2)	0.1642

PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiation therapy; ADT: androgen deprivation therapy; AS: active surveillance; PS group: Patients with prostate cancer detected by PSA-based screening in Hiroshima Prefecture. Non-PS group: Patients with prostate cancer diagnosed at the outpatient office at the Hiroshima University Hospital.

$p = 0.8275$ in stage B and 62.5% and 47.9%, $p = 0.3997$, in stage D, respectively), except in stage C (96.2% and 84.9%, $p = 0.0247$). In all patients, the 5-year OS and CSS of the PS group were 91.3% and 98.2%, respectively, significantly better than those of the non-PS group (86.4%, $p = 0.0178$ and 94.9%, $p = 0.0112$, respectively) (Fig. 2). The multivariate analysis demonstrated that the PSA group was an independent predictive factor for CSS (Table 4).

Discussion

In this study, we found differences in the characteristics and prognosis between the PS group and the non-PS group of prostate cancer patients in the PSA era in Japan.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) has shown the effect of PSA screening on the

Table 4. Multivariate analyses of association between various parameters and cancer-specific survival

	Univariate analysis	Multivariate analysis		
	p value (log-rank)	HR	95% CI	p value
PS group vs. non-PS group	0.0112	3.505	1.302-9.438	0.0131
Age: <70 vs. ≥70	0.1000	1.650	0.611-4.458	0.3229
Initial PSA (ng/mL) <10 vs. 10≥	<0.0001	10.131	2.386-43.022	0.0017
Treatment: prostatectomy vs. others	0.0026	7.500	2.062-7.370	0.0502

PSA: prostate-specific antigen; HR: hazard ratio; CI: confidence interval; PS group: Patients with prostate cancer detected by PSA-based screening in Hiroshima Prefecture. Non-PS group: Patients with prostate cancer diagnosed at the outpatient office at the Hiroshima University Hospital.

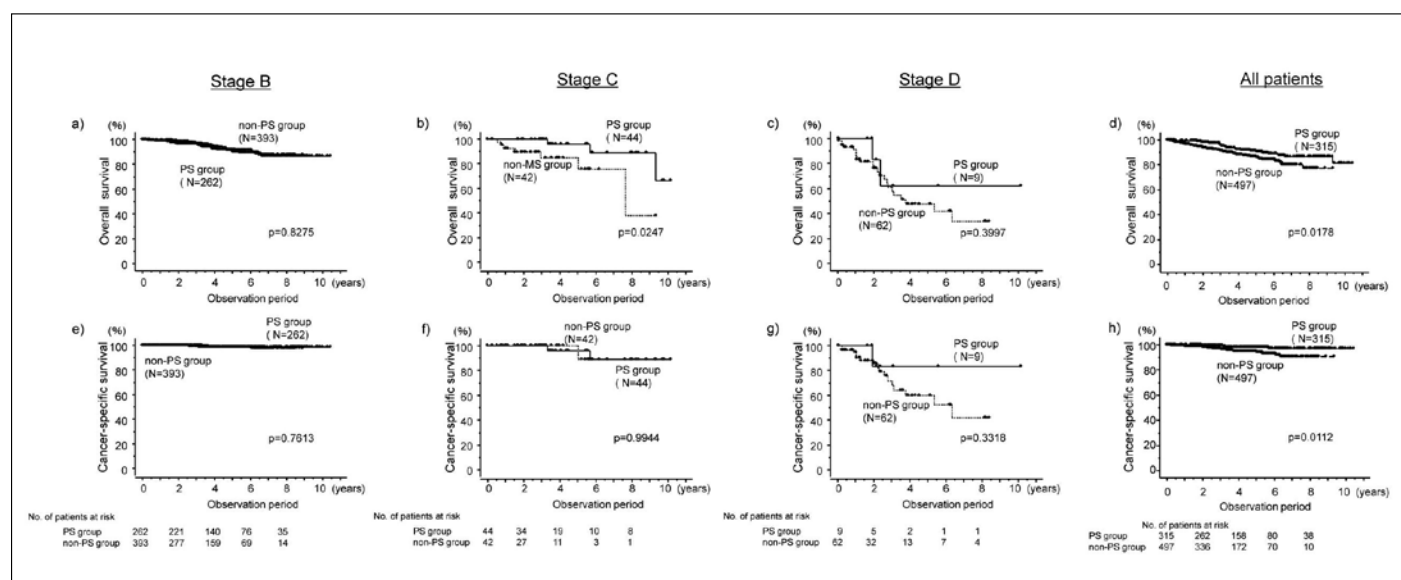


Fig. 2. Overall survival and cancer-specific survival.

reduction of mortality from prostate cancer.⁵⁻⁷ Investigators have demonstrated a reduction in prostate cancer mortality due to PSA screening, and advanced studies have reported the risk predicting prostate cancer using PSA based on data from the ERSPC.⁸⁻¹⁰ On the other hand, the Prostate, Lung, Colorectal, and Ovary (PLCO) screening trial showed no benefit of organized population-based annual screening on mortality.^{11,12} In addition to this discrepancy, the incidence of PSA testing for outpatients has increased in several countries even though there are no present prostate cancer symptoms.¹³⁻¹⁵ This is also evident in Japan, which suggests that early stage prostate cancer may be detected in outpatients as well as with PSA screenings. Therefore, it is critical to compare patients with prostate cancer detected by PSA screening and those diagnosed in outpatient offices to assess the importance of PSA screening in Japan.

As mentioned earlier, we categorized prostate cancer patients into 2 groups: (1) the PS group and the non-PS group. The non-PS group included men who were diagnosed with prostate cancer in outpatient offices and thus includes those who underwent PSA testing regardless of the symptoms related to the prostate. In the PS group, there were fewer patients with high Gleason scores, high PSA, and metastatic diseases (Table 1). Previous studies in Gunma Prefecture and Sweden reported that mass screening could decrease the proportion of metastatic prostate cancer.^{16,17} Our data are consistent with those in these previous studies and demonstrate the effectiveness of prostate cancer screening for early detection of prostate cancer. Other reports have demonstrated that PS decreased not only the rate of metastatic diseases, but also the risk of developing them during the follow-up period.^{18,19} Further observation is required to elucidate such effects in our prostate cancer screening.

In our study, in patients with clinical stage B who were treated with radical prostatectomy, the distribution of D'Amico risk classification in the PS group shifted lower compared with that in the non-PS group (Table 3). Furthermore, bRFS in the PS group was significantly better than that in the non-PS group (Fig. 1). These data indicate that PSA screening can improve the oncologic outcome of prostate cancer in stage B (Fig. 2, parts A, B, C, E, F and G).

To demonstrate the effectiveness of PSA screening for prostate cancer, one of the most crucial points is to show the decrease of mortality. While neither OS nor CSS in the PS group was significantly better than those of the non-PS group in each clinical stage (except OS in stage C), both the OS and CSS of the PS group were significantly better than those of the non-PS group in all patients (Fig. 2, parts D and H), suggesting that fewer patients with a higher stage might lead to a better prognosis in the PS group. Previous studies have demonstrated that longer survival is expected in patients with prostate cancer detected by mass screening.¹⁶ In addition to this evidence, our data indicate that PSA screening might improve the prognosis of prostate cancer patients in the PSA era, in which PSA testing can be performed on all older outpatients even if they do not exhibit any symptoms. Despite the fact that the average age of the PS group was older than the non-PS group, better life expectancy was shown in the PS group. This suggests that PSA screening improves the prognosis in prostate cancer patients.

The difference of distribution of the initial treatments for patients with stage B between the PS group and the non-PS group is a limitation of our study. The ratio of radiation therapy as an initial treatment in the PS-group was significantly higher than that in the non-PS group in all patients and in patients with stage B (Table 2). The reason for this distribu-

tion is that the non-PS group with stage B included patients who underwent brachytherapy using iodine-125 seed, while the PS group did not. Patients in PS group can undergo external beam radiation therapy (EBRT) at the local hospital, while brachytherapy has often been performed for non-PS group diagnosed in the University Hospital in this study. Moreover, the ratio of androgen deprivation therapy as an initial treatment in the PS group was significantly higher than that in the non-PS group. We speculate that the difference of age distribution between the 2 groups was reflected in the choice of the treatment. Specifically, because the PS group included a higher rate of older patients, a higher rate of patients might undergo androgen deprivation therapy. Although older patients with low-risk and localized prostate cancer should undergo active surveillance rather than androgen deprivation therapy, there were few patients who actually underwent it. We should also point out that in addition to the benefits of PSA screening for prostate cancer, there are also some disadvantages. One is unnecessary biopsies and related complications. Data from ERSPC trials showed that 76% of prostate biopsies for an elevated PSA level detected no cancer tissues. Moreover, 3.5% developed a fever, 0.4% experienced urinary retention, and 0.5% required hospitalization for symptoms of urosepsis.²⁰ Another disadvantage is the possibility of unnecessary treatment due to increased diagnosis of early-stage prostate cancer and an increased risk of related complications. Previous randomized control trials have revealed that prostatectomy and radiation therapy are associated with an increased risk for erectile dysfunction and urinary incontinence compared with active surveillance.^{21,22} Insufficient information about treatment options for patients with prostate cancer is one of the most crucial issues in this area and needs to be solved as soon as possible.

Conclusion

We demonstrated that prostate cancer with an earlier stage, lower grade, and better prognosis was shown in PSA screening. Our results indicate that screening in the Hiroshima area should help improve both the OS and CSS of prostate cancer patients through an expected increase of early detection and decrease of high-stage diseases compared with patients whose cancers are detected in outpatient offices. We consider these results to be crucial terms of promoting PSA screening for prostate cancer. However, the present study was retrospective, and the sample size was too small. Additional accumulation of data obtained from more widely spread screening or the prospective study with high volume is required.

Competing interests: Dr. Teishima, Dr. Maruyama, Dr. Mochizuki, Dr. Oka, Dr. Ikeda, Dr. Goto, Dr. Nagamatsu, Dr. Hieda, Dr. Shoji and Dr. Matsubara all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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