Real-world data in elderly men from Yokosuka City 15 years after introducing prostate-specific antigen-based population screening.

TAKUMA NIREI[1], TADASHI TABEI[1], NAOKI SAKAI[2], HIDESHIGE KOH[3], MINORU YOSHIDA[4], ATSUSHI FUJIKAWA[5], HIROKI ITO[1], SOHGO TSUTSUMI[1], SOUICHI FURUHATA[6], SUMIO NOGUCHI[7], MASATAKA TAGURI[8] and KAZUKI KOBAYASHI[1]

[1]Department of Urology, Yokosuka Kyosai Hospital, Yokosuka, Kanagawa 238-8558; [2]Department of Urology, Wakakusa Hospital, Yokohama, Kanagawa 236-8653; [3]Department of Urology, Yokosuka City Uwamachi Hospital, Yokosuka, Kanagawa 238-8567; [4]Department of Urology, Kinugasa Hospital, Yokosuka, Kanagawa 238-8588; [5]Department of Urology, Yokosuka City Hospital, Yokosuka, Kanagawa 240-0195; [6]Furuhata Hinyokika Clinic, Yokosuka, Kanagawa 238-0031; [7]Satomi Jin-Hinyokika Clinic, Yokosuka, Kanagawa 238-0007; [8]Department of Data Science, School of Data Science, Yokohama City University, Yokohama, Kanagawa 236-0027, Japan

Received August 3, 2021; Accepted October 21, 2021

DOI: 10.3892/mco.2021.2471

Abstract. Mass screening based on prostate-specific antigen (PSA) reduces mortality in prostate cancer. However, the effectiveness of this screening in the elderly has not been demonstrated. In the city of Yokosuka, Japan, PSA screening has been conducted since 2001 and the present study examined the real-world status of PSA-based population screening in the elderly. It retrospectively evaluated 1,117 prostate cancer patients >75 years of age. The patients were divided into two groups: The screened group comprising patients diagnosed by PSA-based population screening or workplace screening and PSA follow-up patients at urology clinics; and the non-screened group comprising patients detected by other methods. Overall survival (OS), cancer-specific survival (CSS) and factors contributing to shorter CSS between the groups were compared. In patients >75 years of age, the screened group had significantly longer OS (171 vs. 154 months; P=0.019) and CSS (median not reached; P=0.020) but screening was not an independent factor associated with prolonged OS or CSS on multivariate analysis. The factors contributing to shorten CSS in the elderly were ≥T3 (odds ratio: 3.301 [1.704-6.369], P<0.001), M1 (odds ratio: 4.856 [2.809-8.393], P<0.001) and Gleason score ≥8 (odds ratio: 4.691 [2.479-8.876], P<0.001). In those with metastasis, PSA screening was not associated with prolonged OS or CSS. Real-world data 15 years after introducing PSA-based population screening was not an independent factor for both OS and CSS in multivariate analyses for patients >75 years of age.

Correspondence to: Dr Takuma Nirei, Department of Urology, Yokosuka Kyosai Hospital, 1-16 Yonegahama-Dori, Yokosuka, Kanagawa 238-8558, Japan
Email: tnirei@yokohama-cu.ac.jp

Key words: prostate cancer, early diagnosis, mass screening, mortality, prostatic neoplasm

Introduction

Prostate cancer is the second most commonly diagnosed cancer in men, accounting for 15% of all types of cancer, with an estimated 1.1 million individuals worldwide diagnosed with prostate cancer in 2012 (1). Serum prostate-specific antigen (PSA) level is a useful tumor marker in the diagnosis and follow-up of prostate cancer (2) and PSA is widely used in primary screening measures such as mass screening (3). A prospective observational study in Tyrol, Austria, notes that PSA exposure was 86.6% during the 20-year study period and mortality was 64% lower than expected (4). Various randomized controlled trials (RCTs) have verified the efficacy of prostate cancer screening based on serum PSA screening. Results from the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that in the 55-69 years age group with a median observation period of 13 years, the screening group had a 21% lower mortality rate than the control group (5). An RCT in Gothenburg, Sweden, demonstrated not only significantly reduced mortality from PSA screening, but also lower incidence of advanced cancer (6). In addition, the Rotterdam section of the ERSPC showed that screening every 4 years significantly reduced the risk of developing metastatic cancer (7).

Some discrepancy has been seen in the outcomes of screening, however. In the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Study conducted in the United States, the metastatic cancer rate was low in the control group and the prostate cancer mortality rate was not significantly different from the screening group, although this was because of high contamination of PSA screening in the control group (8-10). The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) in the United Kingdom involving a single invitation to PSA-based screening showed no significant

difference in prostate cancer mortality between the invited and control groups after a median follow-up of 10 years (11). These discrepant outcomes create some confusion around PSA screening, but it is now considered to be beneficial in improving cancer-specific survival based on the findings of a meta-analysis reported in 2018 (12,13). This accumulation of evidence from large RCTs has led to a number of prostate cancer guidelines recommending PSA-based screening for prostate cancer.

The aforementioned large RCTs include men aged between 55 and 69 or 74 years, with little data available on the effectiveness of PSA-based screening for men >70 years of age (7). Moreover, none of these RCTs demonstrate the efficacy of PSA screening for older men, >75 years of age, so routine PSA-based screening for all elderly men has not been recommended. According to the European Association of Urology (EAU) guidelines on prostate cancer, men who have life expectancy within 15 years are unlikely to benefit (14). The Prostate Cancer Early Detection Panel of the US National Comprehensive Cancer Network recommends that men >75 years of age be considered for screening only if in very good health (15). Conversely, the US Preventive Service Task Force recommends that PSA-based screening not be performed in men over 70 years of age (16).

Life expectancy and characteristics of prostate cancer vary by region and race (1), so it is necessary to verify the validity of screening for older adults among Asian populations. Although some studies from China or Korean investigated huge database about PSA screening, their analyses were undergone with single aim, in which comparisons between screened and non-screened men were not revealed (17,18). In Japan, some reports show the effectiveness of PSA-based screening (19-21). However, no studies refer to the upper age limit for PSA screening. In particular, no study demonstrates the usefulness of PSA screening alone at >75 years.

In the city of Yokosuka, Japan, mass screening for prostate cancer based on PSA has been conducted since 2001. Tabei *et al* (22) reported on the overall results in 2020. The study database contains 3,094 patients diagnosed by needle biopsy from 2001 to 2015 in four hospitals (Yokosuka Kyosai Hospital, Yokosuka City Uwamachi Hospital, Kinugasa Hospital and Yokosuka City Hospital) and two urology clinics (Satomi Jin-Hinyokika Clinic and Furuhata Hinyokika Clinic) in the city. Using this database, the present study sought to verify the significance of population screening for elderly men >75 years of age.

Patients and methods

The institutional review boards of all four participating hospitals approved the present study and agreed to provide patient data for the study database. Patients' consent was sought by giving them the choice to opt out of the study through the websites and notice boards of the participating institutions. Patient data was obtained from all institutions.

Patients collection. The present study investigated retrospectively 1,117 patients aged >75 years of age with pathologically diagnosed prostate cancer by needle biopsy at four hospitals and two clinics in Yokosuka city between April 2001 and March 2015. Patients diagnosed accidentally by transurethral resection of the prostate or total cystectomy for bladder cancer were excluded from this study. Patients were followed until prostate cancer-specific mortality, mortality from other causes, or final follow-up on 31 December 2019. Patients without metastasis were classified into four disease risk categories according to the EAU guidelines: Low (T1-T2a and Gleason Score (GS)≤6 and PSA<10 ng/ml, not N1/M1); intermediate (T2b or GS=7 or 10≤PSA ≤20 ng/ml, not N1/M1); high (T2c or GS =8-10 or 20<PSA, not N1/M1); and locally advanced (T3-4 or N1, not M1). Patients with metastasis were classified into the advanced (M1) group.

Definition of 'screened' or 'non-screened' patients. Patients were divided into two groups according to the mode of detection. The screened group included those diagnosed either by PSA-based population screening in the city, other municipalities, or by workplace screening and regular PSA follow-up patients at urology clinics or internal medicine clinics (e.g., benign prostatic hypertrophy, lower urinary tract symptoms or positive on previous screening). The population screening and workplace screening measures used a PSA cut-off of 4.0 ng/ml in serum. The non-screened group consisted of those who had been diagnosed pathologically due to high PSA value in serum examined for other reasons than the above, including pathological fracture, cancers of unknown primary or gross hematuria and lower urinary tract symptoms.

The final decision whether biopsy would be performed is based on consultation with patients exhibiting PSA >4.0 ng/ml about its potential benefits and harms.

Statistical analysis. Age at diagnosis, initial PSA status, tumor stage, risk category, GS, primary treatment, secondary treatment and Charlson Comorbidity score (CS) (23) were compared between the two groups using a two-sided Student's t-test and χ^2 test. Clinical and pathological factors associated with clinical outcomes were assessed using univariate and multivariate analyses with Cox regression analyses to calculate hazard ratios and 95% confidence intervals. Overall mortality was defined as any cause of mortality and cancer specific mortality was defined as mortality from prostate cancer. Cancer-specific and overall survival (OS) rates were calculated using Kaplan-Meier analysis with a log-rank test to compare survival curves between the two groups. Overall mortality was counted as an event in Kaplan-Meier curve for OS and Cancer specific mortality was counted as an event and mortalities from other causes were censored in the curve for CSS. All analyses were carried out using IBM SPSS Statistics for Windows, version 19.0. (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference.

Results

Patients' background. The backgrounds of patients >75 years of age are shown in Table I. A total of 537 were classified in the screened group. Age, initial PSA, GS and CS were not significantly different between the two groups. The screened group showed less advanced cancer with significantly lower N and M stage and risk category (P<0.001), and more T1 and T2 stage compared with the non-screened group (P<0.001). Significantly more patients

Table I. Background of prostate cancer patients >75 years of age who did or did not undergo PSA-based screening.

	Screened group (n=537)		Non-screened group (n=580)		
	Mean/number	Range/(%)	Mean/number	Range/(%)	P-value
Age (years)	78	75-97	79	75-93	0.581
Initial PSA	10.7	3.6-2759	16.1	1.0-13470	0.207
T stage					<0.001
T1	207	(38.5)	173	(29.8)	
T2	173	(32.2)	176	(30.3)	
T3	139	(25.9)	155	(26.7)	
T4	9	(1.8)	4	(0.7)	
N1	25	(4.7)	76	(13.1)	<0.001
M1	44	(8.2)	114	(19.7)	<0.001
Risk category					<0.001
Low	75	(14.0)	56	(9.7)	
Intermediate	143	(26.6)	117	(20.2)	
High	145	(27.0)	130	(22.4)	
Locally advanced	120	(22.3)	129	(22.2)	
Advanced	44	(8.2)	114	(19.7)	
Gleason score					0.209
≤ 6	151	(28.1)	129	(22.2)	
7	183	(34.1)	193	(33.3)	
≥8	186	(34.6)	208	(35.9)	
Charlson Comorbidity score (≥3)	267	(49.7)	278	(47.9)	0.550
Primary treatment					0.003
Watchful waiting/active surveillance	41	(7.6)	24	(4.1)	
Radiation	27	(5.0)	15	(2.6)	
Operation	48	(8.9)	33	(5.7)	
Androgen deprivation therapy	415	(77.3)	489	(84.3)	
Other	6	(1.1)	19	(3.2)	
Cause of mortality	n=133		n=170		0.643
Prostate cancer	29	(21.8)	49	(28.8)	
Other malignancies	28	(21.1)	33	(19.4)	
Pneumonia	14	(10.5)	13	(7.6)	
Stroke	5	(4.4)	8	(4.7)	
Heart failure	4	(3.8)	12	(7.1)	
Chronic respiratory failure	3	(2.3)	2	(1.2)	
Aortic dissection	2	(1.5)	2	(1.2)	
Myocardial infarction	2	(1.5)	1	(0.6)	
Chronic renal failure	2	(1.5)	1	(0.6)	
Other	9	(6.8)	5	(2.9)	
Unknown	35	(26.3)	46	(27.1)	

PSA, prostate-specific antigen.

received androgen deprivation therapy in the non-screened group compared with the screened group (P=0.003).

Overall and cancer-specific survival. OS and CSS in the patients >75 years of age were analyzed by the Kaplan-Meier method (Fig. 1A and B). OS and CSS were significantly longer in the screened group (171 vs. 154 months; P=0.019; P=0.020). OS or CSS among patients with metastasis between the screened and non-screened groups were shown in Fig. 1C and D. There were no significant differences between the two groups (P=0.235, P=0.697).

Cause of mortality. The rate of cancer-specific mortality compared with overall mortality for each risk category

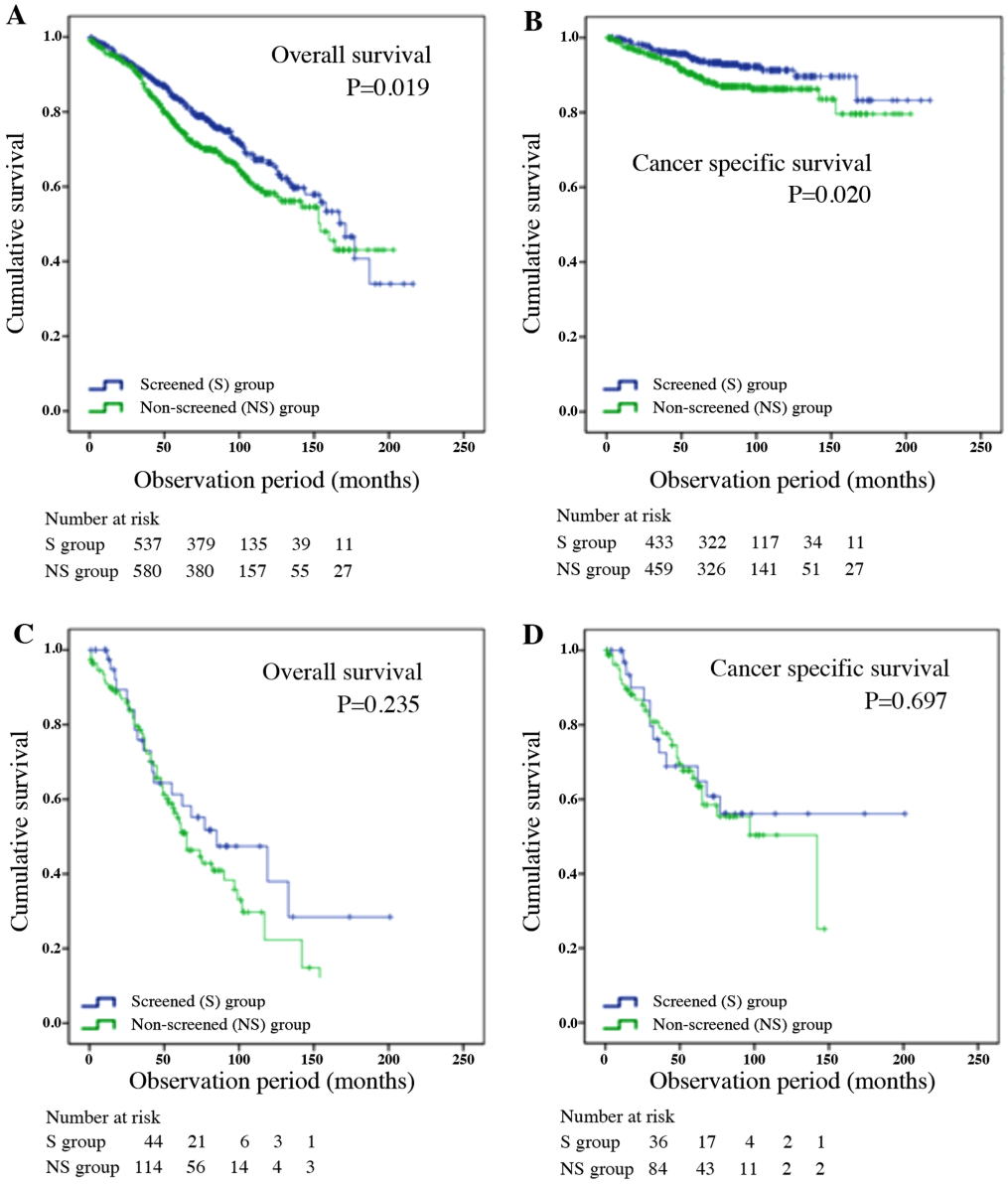

Figure 1. The results of Kaplan-Meier curve. (A) Kaplan-Meier curve of overall survival. (B) Kaplan-Meier curve of cancer-specific survival. (C) Kaplan-Meier curve of overall survival in patients with metastasis. (D) Kaplan-Meier curve of cancer-specific survival in patients with metastasis. S, screened group; NS, non-screened group

was investigated and there were no mortalities in the low risk category in either group. In even locally-advanced risk category, at least two thirds of patients succumbed to another disease. Half of patients in the advanced disease category in the non-screened group succumbed. There were 133 mortalities from other causes in the screening group, of which two succumbed to myocardial infarction (Table I). The most common cause of mortality was prostate cancer, followed by other malignancies in 28 patients and pneumonia in 14 patients. There were 170 mortalities from other causes in the non-examination group, of which one succumbed to myocardial infarction. The most common cause of mortality was prostate cancer in 49 patients, followed by other malignancies in 33 patients and pneumonia in 13 patients. A Chi-square test of the cause of mortality in patients receiving androgen deprivation therapy showed no significant difference (P=0.534) between the screened group and the non-screened group (Table SI) and there was no significant difference (P=0.127) between those who succumbed to prostate cancer and non-prostate cancer. The increase in cardiovascular events associated with androgen deprivation therapy was unclear.

Multivariate analysis. The factors contributing to shortening OS and CSS (Table II) were revealed by multivariate analysis. For OS, these were age [odds ratio: 1.048 (1.018-1.907), P=0.002], PSA≥20 ng/ml [odds ratio: 1.551 (1.134-2.015), P=0.005), ≥T3 (odds ratio: 1.436 [1.081-1.907], P=0.012)], M1 [odds ratio: 1.676 (1.205-2.331), P=0.002], GS≥8 [odds ratio: 1.364 (1.052-1.769), P=0.019] and CS≥3 [odds ratio: 1.884 (1.422-2.390), P<0.001]. For CSS, these were ≥T3 [odds ratio: 3.301 (1.704-6.396), P<0.001], M1 [odds ratio: 4.856 (2.809-8.393), P<0.001] and GS≥8 [odds ratio: 4.691 (2.479-8.876), P<0.001].

Table II. Results of multivariate analysis of overall survival in prostate cancer patients >75 years of age.

	Full model			Reduced model		
	P-value	Odds	95% CI	P-value	Odds	95% CI
Overall survival						
Age	0.003	1.046	1.016-1.078	0.002	1.048	1.018-1.907
PSA ≥20 ng/ml	0.006	1.507	1.128-2.013	0.005	1.511	1.134-2.015
Non-screened group	0.401	1.113	0.867-1.429			
≥T3	0.010	1.454	1.093-1.934	0.012	1.436	1.081-1.907
N1	0.456	0.857	0.571-1.287			
M1	0.003	1.720	1.208-2.449	0.002	1.676	1.205-2.331
Gleason score ≥8	0.014	1.388	1.068-1.803	0.019	1.364	1.052-1.769
Charlson Comorbidity score ≥3	<0.001	1.857	1.432-2.408	<0.001	1.844	1.422-2.390
Cancer-specific survival						
Age	0.345	1.031	0.967-1.100			
PSA ≥20 ng/ml	0.233	1.531	0.760-3.083			
Non-screened group	0.523	1.185	0.704-1.993			
≥T3	0.001	3.065	1.553-6.049	<0.001	3.301	1.704-6.396
N1	0.258	0.692	0.365-1.311			
M1	<0.001	4.745	2.530-8.898	<0.001	4.856	2.809-8.393
Gleason score ≥8	<0.001	4.614	2.404-8.858	<0.001	4.691	2.479-8.876
Charlson Comorbidity score ≥3	0.690	0.902	0.544-1.496			

PSA, prostate-specific antigen; CI confidence interval.

Discussion

In elderly patients >75 years of age, median OS was significantly longer in the screened group compared with the non-screened group (171 vs. 154 months; P=0.019; Fig. 1A and B). Median CSS was not reached in either group, but CSS was significantly longer in the screened group (P=0.020). However, screening was not an independent factor in both OS and CSS in multivariate analyses (Table II).

In the elderly, clinically insignificant types of cancer (e.g., low GS, low T stage and no metastasis), where there are no clinical signs of prostate cancer, is prevalent (24) with a 1.71 increase in odds ratio for every 10 years of age (25). Therefore, it was hypothesized that a number of clinically insignificant cancers were potentially present in the elderly and it was possible that few fatal cancers would contribute to prognosis. PSA screening for elderly men might have more risk of over-diagnosis than that for middle-aged men. The present study found that CS was a significant factor associated with shorter OS (Table II). Moreover, prostate cancer mortalities did not account for a large proportion of all mortalities and even in patients with advanced disease ~50% succumbed other causes. These were consistent with the results of our previous study (22).

The presence of metastasis was the most significant factor associated with shorter CSS in the elderly [odds ratio: 4.856 (2.809-8.393), P<0.001; Table II]. Some guidelines for prostate cancer management are hesitant to recommend PSA screening in elderly men. The authors of the present study expected favorable outcome for screening even for elderly in a previous study (22).

By contrast, the present study found no significant difference in OS or CSS among patients with metastasis between the screened and non-screened groups (Fig. 1C and D). The latest findings for men >75 years of age therefore do not support our previous study (22). It is suspected that this discrepancy is due to the following reasons. In Japan, PSA screening is carried out under the initiative of local governments and not under a national policy, although there are regional differences and consultation is also voluntary for individuals. Median overall age in the Yokosuka City database was high (71 years in the screened group and 73 years in the non-screened group) and prostate cancer with metastasis was more frequent in elderly patients in both the screened (8.2 vs. 5.2%) and non-screened (19.7 vs. 15.0%) groups than in all patients (22). Thus, it is hypothesized that PSA screening in middle-aged men is likely to associated with poor exposure and that cancer was not detected early, so there were a number of cases of advanced cancer in the elderly.

The study database was created in a medical area that covers almost the entire city of Yokosuka and nearby Miura. Using municipal demographics and prostate cancer incidence rates from national databases, the estimated number of prostate cancer patients for the preceding 15 years is ~1,268 for those >75 years of age. The study database contains a number of records for prostate cancer patients, of whom about 88% are >75 years of age. Considering that the average life expectancy of men in Japan was 81 years in 2017, it is estimated that the database covers most elderly patients with prostate cancer in the area.

The present study had some limitations. First, patient information was obtained from the medical records only. The

design was retrospective, so not all patients were followed up fully and some were lost during follow-up. Second, this study included only pathologically diagnosed patients. In real-world settings, some patients with clinically advanced prostate cancer are diagnosed without prostate biopsy and imaging findings. Consequently, the results probably overestimated CSS, especially in the non-screened group. In the screened group, health awareness might have been high and this could pose some bias. Several new treatments for prostate cancer (e.g., abiraterone acetate, enzalutamide and radium-223 chloride) became available during the observation period and there might have been differences in treatment effect depending on the time of observation. Thus, the therapeutic effect could have been underestimated, compared with standard treatment widely used today. Third, almost all patients were Asian. Individual patient backgrounds were searched as much as possible to avoid sample contamination, but it is possible that patients previously exposed to PSA testing are classified in the non-screened group. Moreover, in this database, >90% of cases had undergone some initial treatment since diagnosis and therefore the results of the present study do not represent the natural history of prostate cancer. As s a retrospective study, the validity of PSA screening in the elderly could not be verified. Furthermore, assessments for cost effectivity or quality of line are lacking. From these points of view, PSA screening might have some benefits for elderly individuals. Yet, the data from the present study could not reveal the survival benefit of PSA screening for the patients >75 years old.

Acknowledgements

The authors thank Ms. Ayumi Yokokawa (Assistant, Department of Urology, Yokosuka Kyosai Hospital) for exceptional contributions to the current study.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TN was involved in project development and performed data collection or management, data analysis and writing of the manuscript. TT was involved in project development, data collection, data analysis and editing the manuscript. HI was involved in data collection, data analysis and editing the manuscript. NS, HK, MY, AF, ST, SF and SN performed data collection. MT performed data analysis. KK edited the manuscript and supervised the present study.

Ethics approval and consent to participate

The institutional review boards of all four participating hospitals approved this study and agreed to provide patient data for the study database (approval no. 19-70). Patients' consent was sought by giving them the choice to opt out of the study through the websites and notice boards of the participating institutions.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-E386, 2015.
2. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS and Redwine E: Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 317: 909-916, 1987.
3. Mistry K and Cable G: Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. J Am Board Fam Pract 16: 95-101, 2003.
4. Oberaigner W, Siebert U, Horninger W, Klocker H, Bektic J, Schäfer G, Frauscher F, Schennach H and Bartsch G: Prostate-specific antigen testing in Tyrol, Austria: Prostate cancer mortality reduction was supported by an update with mortality data up to 2008. Int J Public Health 57: 57-62, 2012.
5. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, Kwiatkowski M, Lujan M, Määttänen L, Lilja H, *et al*; ERSPC Investigators: Screening and prostate cancer mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 384: 2027-2035, 2014.
6. Aus G, Bergdahl S, Lodding P, Lilja H and Hugosson J: Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer - results from a prospective, population-based randomized controlled trial. Eur Urol 51: 659-664, 2007.
7. Kerkhof M, Roobol MJ, Cuzick J, Sasieni P, Roemeling S, Schröder FH and Steyerberg EW: Effect of the correction for noncompliance and contamination on the estimated reduction of metastatic prostate cancer within a randomized screening trial (ERSPC section Rotterdam). Int J Cancer 127: 2639-2644, 2010.
8. Pinsky PF, Prorok PC, Yu K, Kramer BS, Black A, Gohagan JK, Crawford ED, Grubb RL and Andriole GL: Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 123: 592-599, 2017.
9. Pinsky PF, Blacka A, Kramer BS, Miller A, Prorok PC and Berg C: Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Clin Trials 7: 303-311, 2010.
10. Shoag JE, Mittal S and Hu JC: Reevaluating PSA testing rates in the PLCO trial. N Engl J Med 374: 1795-1796, 2016.
11. Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, Lane JA, Noble S, Oliver SE, Evans S, *et al*; CAP Trial Group: Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: The CAP randomized clinical trial. JAMA 319: 883-895, 2018.
12. Fenton JJ, Weyrich MS, Durbin S, Liu Y, Bang H and Melnikow J: Prostate-specific antigen-based screening for prostate cancer: Evidence report and systematic review for the US Preventive Services Task Force. JAMA 319: 1914-1931, 2018.
13. Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, Agoritsas T and Dahm P: Prostate cancer screening with prostate-specific antigen (PSA) test: A systematic review and meta-analysis. BMJ 362: k3519, 2018.
14. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, Fossati N, Gross T, Henry AM, Joniau S, *et al*: EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. Eur Urol 71: 618-629, 2017.
15. Carroll PR, Parsons JK, Andriole G, Bahnson RR, Barocas DA, Castle EP, Catalona WJ, Dahl DM, Davis JW, Epstein JI, *et al*: NCCN clinical practice guidelines prostate cancer early detection, version 2.2015. J Natl Compr Canc Netw 13: 1534-1561, 2015.

16. Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, Doubeni CA, Ebell M, Epling JW Jr, Kemper AR, *et al*; US Preventive Services Task Force: Screening For Prostate Cancer: US preventive services task force recommendation statement. JAMA 319: 1901-1913, 2018.
17. Mok Y, Kimm H, Shin SY, Jee SH and Platz EA: Screening prostate-specific antigen concentration and prostate cancer mortality: The Korean Heart Study. Urology 85: 1111-1116, 2015.
18. Liu Y, Xiao G, Zhou JW, Yang JK, Lu L, Bian J, Zhong L, Wei QZ, Zhou QZ, Xue KY, *et al*: Optimal starting age and baseline level for repeat tests: Economic concerns of psa screening for chinese men - 10-year experience of a single center. Urol Int 104: 230-238, 2020.
19. Sakai N, Taguri M, Kobayashi K, Noguchi S, Ikeda S, Koh H, Satomi Y and Furuhata A: Clinical outcomes of prostate cancer patients in Yokosuka City, Japan: A comparative study between cases detected by prostate-specific antigen-based screening in Yokosuka and those detected by other means. Int J Urol 22: 747-752, 2015.
20. Okihara K, Kitamura K, Okada K, Mikami K, Ukimura O and Miki T: Ten year trend in prostate cancer screening with high prostate-specific antigen exposure rate in Japan. Int J Urol 15: 156-161, 2008.
21. Ito K, Kakehi Y, Naito S and Okuyama A; Japanese Urological Association: Japanese Urological Association guidelines on prostate-specific antigen-based screening for prostate cancer and the ongoing cluster cohort study in Japan. Int J Urol 15: 763-768, 2008.
22. Tabei T, Taguri M, Sakai N, Koh H, Yosida M, Fujikawa A, Nirei T, Tsutsumi S, Ito H, Furuhata S, *et al*: Does screening for prostate cancer improve cancer-specific mortality in Asian men? Real-world data in Yokosuka City 15 years after introducing PSA-based population screening. Prostate 80: 824-830, 2020.
23. Charlson ME, Pompei P, Ales KL and MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 40: 373-383, 1987.
24. Rebbeck TR and Haas GP: Temporal trends and racial disparities in global prostate cancer prevalence. Can J Urol 21: 7496-7506, 2014.
25. Bell KJ, Del Mar C, Wright G, Dickinson J and Glasziou P: Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer 137: 1749-1757, 2015.