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Influence of repeated prostate-specific antigen screening on treatment pattern in a country with a limited social perception of prostate cancer: Korean national wide observational study

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Purpose: To investigate the real-world prevalence of repeated prostate-specific antigen (PSA) screening in Korea and its influence on the treatment pattern of the prostate cancer (PCa) over the last decade, during which PCa has become the 3rd most popular male cancer and PSA test has gained minimal social interest.

Materials and Methods: From Korean National Health Insurance Service data, men with newly diagnosed PCa from 2008 through 2016 were identified, then the treatment modalities between the repeated PSA screening (defined as at least three PSA tests during minimal 2 years before registration) and non-screening groups (when the first PSA test was performed within 3 months before registration) were compared.

Results: Among 73,280 men with PCa, only 27.7% met the criteria for screening. In contrast with the continuous increase in the screening population from 334 men in 2008 to 5,049 men in 2016, the non-screening population remained low at 1,543 men in 2008 and 1,819 men in 2016 ($p<0.001$). During these periods, more patients underwent local therapy (prostatectomy or radiation) in the screening population compared to their non-screened counterparts (59.8% vs. 46.7%, $p<0.001$), and fewer patients underwent systemic therapy (chemotherapy or hormone) (40.2% vs. 53.3%, $p<0.001$). Multivariate analysis adjusting other variables demonstrated 2-fold higher mortality in the non-screening population (hazard ratio=2.050, $p<0.0001$).

Conclusions: Among the patients newly diagnosed with PCa, only about a quarter received repeated PSA screening. However, these patients showed a higher probability of local treatment than the systemic one in comparison with non-screened counterparts.

Keywords: Mass screening; Prostate specific antigen; Prostatic neoplasms

INTRODUCTION

The socio-economic benefit of prostate-specific antigen (PSA) screening for the general population is still under debate [1]. Two representative randomized clinical trials (RCTs) for large populations conducted in the US [2] and Europe [3] revealed incompatible results regarding the effect of PSA screening on increasing the survival rate of prostate cancer

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(PCa), even though PCa was the most common malignant disease and a leading cause of death in both regions. Since the initial publication of these RCTs, their conflicting results and prohibitive screening population requirements have long deterred the use of PSA screening among the general population, particularly in nations with a relatively lower incidence of PCa [4,5].

In 2000, PCa became the 10th most common malignant disease in the Korean male population [6]. Despite its incidence increases in the last two decades, PCa is only the 4th most common malignant disease in Korea according to a recently updated national report [7]. Therefore, the social perception of PCa has lagged, which has diminished the usefulness of PSA testing as a screening strategy. Due to the different epidemiologic background of Koreans and limited social awareness of PCa compared to Western countries [8], the PSA test is not routinely performed in regular checkups for males in Korea, in contrast with other prevalent malignant diseases such as stomach, colon, and lung cancers [7].

The purpose of this study was to investigate the real-world prevalence of repeated PSA screening in Korea as well as compare the treatment pattern for PCa between screening and non-screening populations over the last decade, during which PCa has become the 4th most common male cancer and PSA screening has gained minimal social interest among the general population [6].

MATERIALS AND METHODS

1. Data source

Data used in this study were obtained from the Korean National Health Insurance Service (NHIS), which covers approximately 98% of its population and provides universal health coverage. The Korean NHIS database not only includes almost all medical data, including diagnostic codes, procedures, prescription drugs, and outcomes (deaths), it also includes socio-demographic information such as age, health insurance premiums, and residential area. However, NHIS does not provide information on the biological severity of malignant diseases, including serum PSA level, tumor stage, and cellular grade. All personal identification numbers are encrypted before data processing to comply with the privacy guidelines of the Health Insurance Portability and Accountability Act. All study procedures and ethical aspects were approved by the Institutional Review Board of the Yeungnam University Medical Center (approval number: YUMC 201805027).

2. Study population and operational definition of each group of interest

Patients who were newly diagnosed with PCa and registered in the NHIS with an International Classification of Disease-10 code of C61 each year between 2006 and 2017 were recruited for this study. To compare the PSA screening population with data from the non-screening population, we exclusively defined the screening group as having done at least three PSA tests during minimal 2 years before registering PCa in the NHIS. Patients were categorized into the PSA non-screening group if their first PSA test was performed within 3 months before NHIS registration. Radical prostatectomy (RP), including open and laparoscopic approaches, was identified using the codes for reimbursement (R3950 and R3960). Robot-assisted radical prostatectomy (RARP), which was not reimbursed by the NHIS, was operationally defined as the absence of a surgery code despite the presence of general anesthesia code 'L1211') and postoperative pathologic examination codes (code 'C5500', 'C5504', 'C5505', 'C5508', 'C5918', or 'C5919'), among the patients who previously have code C61, as well as V193/194 [9]. Radiation therapy (RT) included all types of radiation modalities, including conformal and intensity-modulated RT. As for chemotherapy (CT), docetaxel and estramustine were the only approved agents during the study period and were selectively investigated.

Based on the definition of the repeated PSA screening population, which requires a minimum of 2 years of consecutive PSA testing, data from 2008–2016 were used for the final analysis. To trace the treatment patterns of both populations as well as their combination yearly, repeatable management, including hormone therapy (HT), CT, and RT, were analyzed by per-incident analysis.

3. Study design and outcome measurement

Epidemiologic characteristics and selected treatments between the screening and non-screening groups were compared. The primary endpoints were 1) to determine the prevalence of PSA screening among PCa patients on a yearly basis and 2) to compare treatment patterns, including local and systemic treatments, between screening and non-screening populations. The secondary endpoint was to compare overall survival (OS) between the two groups regardless of the cause of death, which was not available in the current version of the NHIS data.

4. Statistical analysis

To compare the characteristics and outcomes between each group, Student's t-test was used for continuous variables, and the chi-square test was used for binary and cat-

Table 1. The characteristics of the patients enrolled

Variable	Total (n=35,254)	PSA screening group	PSA non-screening group	p-value
Age (y)	74.99±8.49	75.40±7.47	73.67±8.49	<0.001
<75	18,267	10,244 (50.43)	8,023 (53.70)	<0.001
≥75	16,987	10,070 (49.57)	6,917 (46.30)	
Residential area				
Urban	30,515	17,706 (87.16)	12,809 (85.74)	<0.001
Rural	4,739	2,608 (12.84)	2,131 (14.26)	
Income level				
Lower 20% (I)	15,023	8,800 (43.32)	6,223 (41.65)	<0.001
Upper 80%	18,003	10,065 (49.55)	7,938 (53.13)	<0.001
II	6,860	3,808 (18.75)	3,052 (20.43)	
III	4,175	2,297 (11.31)	1,878 (12.57)	
IV	3,244	1,835 (9.03)	1,409 (9.43)	
V (highest)	3,724	2,125 (10.46)	1,599 (10.70)	
Unknown	2,228	1,449 (7.13)	779 (5.21)	
Total	35,254	20,314 (57.62)	14,940 (42.38)	

Values are presented as mean±standard deviation, number only, or number (%).
PSA, prostate-specific antigen.

egorical variables. Cancer incidence rates were calculated per 1,000 person-years. To compare trends between PSA screening and non-screening populations as well as assess the association between variables with two categories, the Cochran-Armitage Trend test was utilized. Two-sided p-values <0.05 were considered to be statistically significant. All statistical analyses were performed using SAS software (SAS Institute, Cary, NC, USA).

RESULTS

1. Incidence, epidemiologic characteristics, and trend of PSA screening in Korea

Among the 73,280 men with PCa that registered annually during 2008–2016, only 27.7% (20,314 men) were classified in the repeated PSA screening group based on the above operational definition. The percentage of patients that satisfied non-screening criteria was 20.4% (14,940 men), and about half of the recruited patients (51.9%, 38,026 men) were not classified into either group. The characteristics of the screening and non-screening groups are summarized in Table 1. Screened parents tended to be older with a higher proportion of patients with the following characteristics: over 75 years (49.6% vs. 46.3%), living in an urban area (87.2% vs. 85.7%), and a lower income below 20% on average (43.3% vs. 41.7%) in comparison with their non-screened counterparts.

During the study period, the prevalence of repeated PSA screening increased steadily without any recession, as shown in Table 2. In contrast with the continuous increase in the screening population from 334 men in 2008 to 5,049 men in 2016, the non-screening population remained low at 1,543 men in 2008 and 1,819 men in 2016, constituting a distinct difference (Cochran-Armitage Trend test, p<0.001). This increase in screening was prominent in all subgroups regardless of the age cut-off of 75 years, area of residence, and income cut-off of 20%.

2. The difference in treatment pattern between screening and non-screening groups

During the study period, 297,147 treatments for PCa were identified, with 143,990 treatments (48.5%) in the screening population and 153,157 treatments (51.5%) in the non-screening population. Categorization according to treatment modalities is summarized in Table 3. In comparing the groups, more patients in the screening group underwent local therapy for PCa, including RP, RARP, and RT, compared to the non-screening population (86,139 vs. 71,584 p<0.001), and fewer patients underwent systemic therapy, including chemotherapy or prolonged-hormonal therapy (57,851 vs. 81,573, p<0.001). This trend was similarly observed across all subgroup populations (Table 3). The serial trends in the yearly incidence of each local treatment are summarized in Fig. 1. For all three local treatment modalities, the PSA screening population outnumbered the non-screening population and continuously increased annually.

3. Comparison of mortality between PSA screening and non-screening groups

The mortality rate of the non-screening population was almost two times that of the screening group (34.3% vs. 18.9%,

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Table 2. The trend of PSA screening in each year

Year	Total enrolled				Age, <75 yr				Age, ≥75 yr			
	Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value
2008	1,877	334 (17.8)	1,543 (82.2)	<0.001	782	108 (13.8)	674 (86.2)	<0.001	1,095	226 (20.6)	869 (79.4)	<0.001
2009	2,546	892 (35.0)	1,654 (65.0)		992	276 (27.8)	716 (72.2)		1,554	616 (39.6)	938 (60.4)	
2010	2,826	1,152 (40.8)	1,674 (59.2)		1,226	449 (36.6)	777 (63.4)		1,600	703 (43.9)	897 (56.1)	
2011	3,495	1,778 (50.9)	1,717 (49.1)		1,524	683 (44.8)	841 (55.2)		1,971	1,095 (55.6)	876 (44.4)	
2012	3,886	2,182 (56.2)	1,704 (43.8)		1,811	941 (52.0)	870 (48.0)		2,075	1,241 (59.8)	834 (40.2)	
2013	4,344	2,682 (61.7)	1,662 (38.3)		2,261	1,293 (57.2)	968 (42.8)		2,083	1,389 (66.7)	694 (33.3)	
2014	4,551	2,911 (64.0)	1,640 (36.0)		2,484	1,511 (60.8)	973 (39.2)		2,067	1,400 (67.7)	667 (32.3)	
2015	4,861	3,334 (68.6)	1,527 (31.4)		2,802	1,834 (65.5)	968 (34.5)		2,059	1,500 (72.9)	559 (27.1)	
2016	6,868	5,049 (73.5)	1,819 (26.5)		4,385	3,149 (71.8)	1,236 (28.2)		2,483	1,900 (76.5)	583 (23.5)	
Total	35,254	20,314 (57.6)	14,940 (42.4)		18,267	10,244 (56.1)	8,023 (43.9)		16,987	10,070 (59.3)	6,917 (40.7)	

Year	Total enrolled				Residential area, Urban				Residential area, Rural			
	Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value
2008	1,877	1,543 (82.2)	240 (12.8)	<0.001	1,637	293 (17.9)	1,344 (82.1)	<0.001	240	41 (17.1)	199 (82.9)	<0.001
2009	2,546	1,654 (65.0)	325 (12.8)		2,221	801 (36.1)	1,420 (63.9)		325	91 (28.0)	234 (72.0)	
2010	2,826	1,674 (59.2)	397 (14.0)		2,429	1,010 (41.6)	1,419 (58.4)		397	142 (35.8)	255 (64.2)	
2011	3,495	1,717 (49.1)	467 (13.4)		3,028	1,564 (51.7)	1,464 (48.3)		467	214 (45.8)	253 (54.2)	
2012	3,886	1,704 (43.8)	544 (14.0)		3,342	1,897 (56.8)	1,445 (43.2)		544	285 (52.4)	259 (47.6)	
2013	4,344	1,662 (38.3)	570 (13.1)		3,774	2,338 (62.0)	1,436 (38.0)		570	344 (60.4)	226 (39.6)	
2014	4,551	1,640 (36.0)	627 (13.8)		3,924	2,532 (64.5)	1,392 (35.5)		627	379 (60.4)	248 (39.6)	
2015	4,861	1,527 (31.4)	662 (13.6)		4,199	2,887 (68.8)	1,312 (31.2)		662	447 (67.5)	215 (32.5)	
2016	6,868	1,819 (26.5)	907 (13.2)		5,961	4,384 (73.5)	1,577 (26.5)		907	665 (73.3)	242 (26.7)	
Total	35,254	14,940 (42.4)	4,739 (13.4)		30,515	17,706 (58.0)	12,809 (42.0)		4,739	2,608 (55.0)	2,131 (45.0)	

Year	Total enrolled				Income level, Lower 20%				Income level, Upper 80%			
	Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value
2008	1,743	284 (16.3)	1,459 (83.7)	<0.001	813	154 (18.9)	659 (81.1)	<0.001	930	130 (14.0)	800 (86.0)	<0.001
2009	2,390	815 (34.1)	1,575 (65.9)		1,131	394 (34.8)	737 (65.2)		1,259	421 (33.4)	838 (66.6)	
2010	2,650	1,061 (40.0)	1,589 (60.0)		1,256	537 (42.8)	719 (57.2)		1,394	524 (37.6)	870 (62.4)	
2011	3,227	1,611 (49.9)	1,616 (50.1)		1,528	779 (51.0)	749 (49.0)		1,699	832 (49.0)	867 (51.0)	
2012	3,644	2,032 (55.8)	1,612 (44.2)		1,709	997 (58.3)	712 (41.7)		1,935	1,035 (53.5)	900 (46.5)	
2013	4,059	2,481 (61.1)	1,578 (38.9)		1,832	1,147 (62.6)	685 (37.4)		2,227	1,334 (59.9)	893 (40.1)	
2014	4,268	2,718 (63.7)	1,550 (36.3)		1,900	1,213 (63.8)	687 (36.2)		2,368	1,505 (63.6)	863 (36.4)	
2015	4,540	3,107 (68.4)	1,433 (31.6)		2,018	1,434 (71.1)	584 (28.9)		2,522	1,673 (66.3)	849 (33.7)	
2016	6,505	4,756 (73.1)	1,749 (26.9)		2,836	2,145 (75.6)	691 (24.4)		3,669	2,611 (71.2)	1,058 (28.8)	
Total	33,026	18,865 (57.1)	14,161 (42.9)		15,023	8,800 (58.6)	6,223 (41.4)		18,003	10,065 (55.9)	7,938 (44.1)	

Values are presented as number only or number (%).
PSA, prostate-specific antigen.

Table 3. The summary of treatment pattern in each subgroup based on the PSA testing

Prostate cancer treatments	Total				Age, <75 yr				Age, ≥75 yr				Residential area, Urban				Residential area, Rural				p-value (urban vs. rural)	Income level, Lower 20%				Income level, Upper 80%				p-value (lower 20% vs. upper 80%)
	Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value	p-value (<75 vs. ≥75)	Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value		Total	PSA screening group	Non-screening group	p-value	Total	PSA screening group	Non-screening group	p-value	
CT	1,434 (0.5)	296 (0.2)	1,138 (0.7)	<0.001	948 (0.7)	176 (0.3)	772 (1.0)	<0.001	486 (0.3)	120 (0.1)	366 (0.5)	<0.001	<0.001	1,221 (0.5)	243 (0.2)	978 (0.7)	<0.001	213 (0.5)	53 (0.3)	160 (0.7)	<0.001	<0.001	437 (0.4)	101 (0.2)	336 (0.5)	<0.001	888 (0.6)	178 (0.3)	710 (0.9)	<0.001	<0.001
HT	138,018 (46.4)	57,560 (40.0)	80,458 (52.5)		43,319 (31.3)	13,915 (22.8)	29,404 (38)		94,699 (59.7)	43,645 (52.7)	51,054 (67.3)			116,780 (45.5)	49,563 (39.5)	67,217 (51.4)		21,238 (52.1)	7,997 (43.3)	13,241 (59.5)			56,820 (45.9)	23,375 (38.7)	33,445 (52.6)		68,429 (45.2)	26,845 (37.9)	41,584 (51.6)		
RT	144,593 (48.7)	78,220 (54.3)	66,373 (43.3)		85,016 (61.4)	41,444 (67.8)	43,572 (56.3)		59,577 (37.5)	36,776 (44.4)	22,801 (30.1)			126,903 (49.5)	68,754 (54.8)	58,149 (44.4)		17,690 (43.4)	9,466 (51.3)	8,224 (36.9)			61,200 (49.4)	33,587 (55.6)	27,613 (43.5)		75,182 (49.6)	39,691 (56.0)	35,491 (44.0)		
RP	6,205 (2.1)	3,784 (2.6)	2,421 (1.6)		4,168 (3.0)	2,593 (4.2)	1,575 (2.0)		2,037 (1.3)	1,191 (1.4)	846 (1.1)			5,388 (2.1)	3,305 (2.6)	2,083 (1.6)		817 (2.0)	479 (2.6)	338 (1.5)			2,233 (1.8)	1,354 (2.2)	879 (1.4)		3,554 (2.3)	2,159 (3.0)	1,395 (1.7)		
RARP	6,925 (2.3)	4,135 (2.9)	2,790 (1.8)		4,999 (3.6)	2,976 (4.9)	2,023 (2.6)		1,926 (1.2)	1,159 (1.4)	767 (1.0)			6,120 (2.4)	3,663 (2.9)	2,457 (1.9)		771 (1.9)	472 (2.6)	299 (1.3)			3,216 (2.6)	1,961 (3.2)	1,255 (2.0)		3,481 (2.3)	2,037 (2.9)	1,444 (1.8)		
Systemic (CT+HT)	139,424 (46.9)	57,851 (40.2)	81,573 (53.3)	<0.001	44,241 (32.0)	14,086 (23.1)	30,155 (39.0)	<0.001	95,183 (60.0)	43,765 (52.8)	51,418 (67.8)	<0.001	<0.001	117,974 (46.0)	49,801 (39.7)	68,173 (52.1)	<0.001	21,450 (52.7)	8,050 (43.6)	13,400 (60.2)	<0.001	<0.001	57,247 (46.2)	23,475 (38.9)	33,772 (53.2)	<0.001	69,308 (45.7)	27,019 (38.1)	42,289 (52.5)	<0.001	0.015
Local (RT+ RP+ RARP)	157,723 (53.1)	86,139 (59.8)	71,584 (46.7)		94,183 (68.0)	47,013 (76.9)	47,170 (61.0)		63,540 (40.0)	39,126 (47.2)	24,414 (32.2)			138,443 (54.0)	75,722 (60.3)	62,721 (47.9)		19,280 (47.3)	10,417 (56.4)	8,863 (39.8)			66,649 (53.8)	36,902 (61.1)	29,747 (46.8)		82,217 (54.3)	43,887 (61.9)	38,330 (47.5)		

Values are presented as number (%).
PSA, prostate-specific antigen; CT, chemotherapy; HT, hormone therapy; RT, radiation therapy; RP, radical prostatectomy; RARP, robot-assisted radical prostatectomy.

p<0.001). Mortality was also higher in rural areas (30.7% vs. 24.5%) and men with a lower income (25.2% vs. 23.6%). Multivariate analysis adjusting for all three variables showed that the mortality of the non-screening population was about two times that of their screened counterparts (hazard ratio=2.050, p<0.0001; Table 4).

DISCUSSION

Serum PSA testing plays a pivotal role in the diagnosis of PCa, especially for an early diagnosis before symptoms of systemic disease spread have developed. Indeed, a population-based screening cohort study previously reported that the proportion of metastatic PCa detected by PSA screening gradually decreased as the exposure rate to screening increased [10]. Based on Japanese national reports in which PSA screening was strongly advocated, the rate of metastatic diseases reported among all recorded cases decreased from 21.3% in 2000 to 11.6% in 2004 [11,12]. Even though clinical trials for PSA screening in Western countries have demonstrated limited benefits with regards to patient survival, widespread screening might contribute to a more aggressive attitude towards PCa management. In combination with the development of novel medications, recent trends have shown a continuous decrease in the PCa mortality rate in Western countries. However, how these statements apply to the Asian population remains unclear when one considers the low incidence of PCa and less exposure to PSA screening in Asia due to the limited perception of PCa at the societal level.

The ultimate aim of population screening for cancer is to reduce cancer-specific mortality. However, the macroscopic consequence of PSA screening for the general population can be quite different based on the exposure rate and manifestation of racial differences in PCa incidence. As shown in the reported mismatch between large-scale population-based screening cohort studies in the US [2] and Europe [3], PSA screening may result in over-diagnosis and over-treatment in countries with established histories of PSA test. In contrast, PSA screening may result in earlier detection of PCa as well as significantly reduce the metastatic spread in countries in which PSA screening has not been widely adopted yet [10,13]. Although it is impossible to compare exposure rates to PSA screening among countries, a PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) study carried out in the US reported that over 90% of men in the 'usual care' arm underwent some degree of PSA testing in 2009 [14]. In the real world, 75% of those aged 50 years or older have had a PSA test in the US, and 54% of them reported an up-to-date PSA screening [15]. Similarly, a Japanese hospital-

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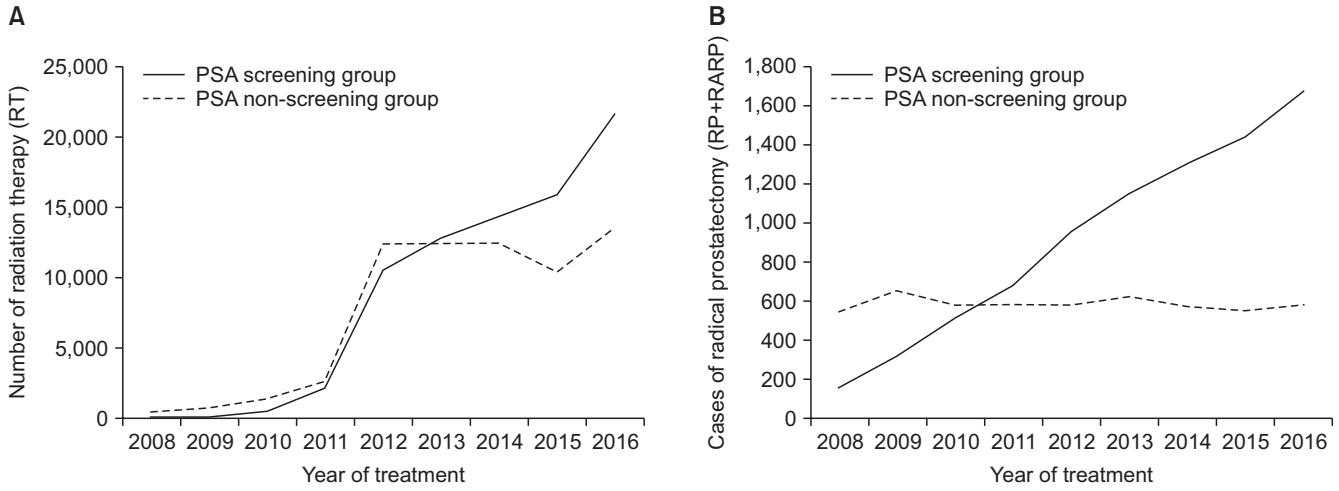

Fig. 1. The yearly basis trend of local treatment in each group: (A) radiation therapy (RT), (B) radical prostatectomy (RP) including robot-assisted radical prostatectomy (RARP). PSA, prostate-specific antigen.

Table 4. The summary of mutivarible analysis on overall survival

Variable	p-value	Hazard ratio	95% Confidence interval	
			Lower	Upper
PSA screening		Reference		
Non-screening	<0.0001	2.050	1.944	2.161
Age (y)				
<75		Reference		
≥75	<0.0001	3.519	3.331	3.719
Residential area				
Urban		Reference		
Rural	<0.0001	1.254	1.165	1.349
Income level				
Upper 80%		Reference		
Lower 20%	<0.0001	1.218	1.218	1.356

PSA, prostate-specific antigen.

based cohort study reported that 73.5% of PCa patients aged 55–69 years were detected by PSA screening in 2014 [16]. In contrast, even in PSA screening populations, the proportion of metastatic disease was reported up to be 26.1% in Chinese in 2004 where the screening exposure to PSA was lower than in Western countries [17]. In the same year, only 15% of Korean men over 50 years reported as having been screened during the previous 2 years [13].

Given the relatively long survival rate of PCa and increasing lifespan of South Korean males (almost 80 years on average), we surmised that the advantage conferred by PSA screening for the general population may not be revealed in the form of prolonged cancer-specific survival but instead as a change in treatment pattern. We thus traced the impact of repeated PSA screening on the treatment pattern of PCa in Korea. In this national wide study that recruited the entire PCa population of South Korea, only a quarter of them was found to have undergone PSA screening. However, this study also demonstrated that repeated PSA screening was associated with a higher chance of local treatment regardless of available treatment modalities as well as a lower chance of systemic therapy using hormones or chemotherapy. Besides, the OS, the secondary endpoint of this study, was about two times higher in the screening population compared to the non-screening population. These results suggest that repeated PSA screening of the Korean population during the study period resulted in earlier detection in the locally controllable stage.

Given the increasing incidence and prevalence of PCa in Asian countries, the outcome of this study suggests the clinical relevance of PSA testing as a regular check-up modality for Korean males. At present, PSA sampling is not widely available as a regular checkup procedure even in high incidence countries such as the US, UK, and Japan due to lack of evidence supporting its socio-economic benefits. Considering the very high incidence of PSA testing in those countries with an enhanced social awareness on PCa, the outcomes of randomized clinical trials from Western countries [2,3], including the most recent one [18], cannot be interpreted as non-preferred evidence against PSA screening for the general Asian population. Indeed, a Korean observational study demonstrated that ADT is still the most frequently chosen treatment for the initial management of PCa, reflecting the advanced stage of the disease. While the data have shown a decrease in ADT frequency from 60.3% in 2003, it was still utilized as the primary treatment in 45.5% of patients in 2013 [19]. In a national NHIS study, Kang et al. [9] reported that 54.9% of registered PCa patients received ADT in 2014,

which represents a 14.9% decrease in comparison with 2005.

The authors are well aware of the limitations of this study. First and most importantly, the current version of the Korean NHIS data does not provide basic information on risk stratification of PCa, including the serum level of PSA, clinical stage, and Gleason score or grade. Accordingly, we traced serial changes in the treatment pattern, which reflects the aggressiveness of the disease. However, since the majority of local procedures were carried out at a high-throughput academic center in Korea and most available guidelines do not recommend local treatment for oligometastatic diseases during the study period, we surmise that our contemporary data are sufficient to simply dichotomize the modality into systemic and local treatments. Second, with regard to the operational definition of repeated PSA screening, there is no consensus in the literature or contemporary guidelines. While our data contrast the characteristics of screening and non-screening patients from an epidemiologic point of view, about half of the patients could not be classified according to these definitions. Thus, our results may not be reproducible when using different definitions for the screening and non-screening groups. However, we do not think a single PSA test possesses similar clinical relevance as a serial check-up when it comes to clinical decisions such as implantation of prostate biopsy which has been reported by a recent trial [18,20]. Third, the current version of the NHIS does not contain information on cancer-specific survival rates. Thus, we reluctantly substituted data on OS. The advanced version of the NHIS is supposed to have information on cancer-specific survival rates. However, given that the reported average disease period for registered PCa patients is less than 5 years [7], this period might not be sufficient to expect prolongation of survival in PCa patients. Four, while the majority of randomized clinical trials on the efficacy of PSA test as a screening tool for PCa demonstrated a significant decrease in the incidence of advanced disease, the researchers consistently reported an increased incidence in the localized disease, which reflects the higher probability of low-risk PCa dominantly screened by this strategy [21]. The debate over the efficacy of PSA based screening is still ongoing, requires further cut-offs to improve the specificity of clinically significant PCa [5]. Five, because the current version of NHIS did not allow to capture the patients who previously had PSA testing performed through a private, non-insured health check-up, some of the non-screened group in this study may have proper PSA screening in the real world. However, the proportion of the patient with highest income level who might have the highest opportunity to take part in the private check-up was not much different between groups (10.46% in PSA screening group vs. 10.70% in the non-screened group, Table 1). Six, although the mortality rate was about two times higher in the non-screening group, a causal relationship was not clear from the observational study design. Furthermore, the variables which allow being investigated by the current version of NHIS look superficial to extract a solid conclusion. Thus, these results should be considered as hypothesis-generating and will spur further investigations into PSA screening in societies with limited social awareness of the disease.

CONCLUSIONS

Among patients newly diagnosed with PCa in Korea, only about a quarter were found to have undergone repeated PSA screening. However, the screening population showed a higher probability of local than systemic treatment, which reflects an earlier disease stage at the time of diagnosis in comparison with their non-screened counterparts.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Young Hwii Ko. Data acquisition: Young Hwii Ko. Statistical analysis: Young Hwii Ko and Sang Won Kim. Data analysis and interpretation: Young Hwii Ko and Sang Won Kim. Drafting of the manuscript: Young Hwii Ko. Critical revision of the manuscript: Young Hwii Ko. Obtaining funding: Young Hwii Ko. Administrative, technical, or material support: Young Hwii Ko. Supervision: Young Hwii Ko. Approval of the final manuscript: Young Hwii Ko.

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