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The Use of 5-Alpha Reductase Inhibitors Improves the Detection of Prostate Cancer by Increasing Opportunities for Repeated Prostate-Specific Antigen Testing: A Decade-Long (2007–2016) Nationwide Observational Study in Korea

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Purpose: The aim of this study was to investigate the influence of taking 5-alpha reductase inhibitors (5ARIs) on the detection of prostate cancer (PCa), considering the reported low uptake of prostate-specific antigen (PSA) testing among Korean men.

Materials and Methods: From Korean National Health Insurance Sharing Service data, the number of men older than 40 years who were prescribed 5ARIs from 2007 through 2016 was identified. The association of 5ARI prescriptions with newly registered PCa was analyzed.

Results: In total, 1,528,128 men who took 5ARIs for a mean of 1.523±2.221 years were identified. Among 138,614 patients with PCa, 68,529 (49.4%) took 5ARIs and 70,085 did not. The incidence of PCa was significantly higher in the 5ARI group than in the non-5ARI group during all study years ($p<0.001$) except for 2007. Adjusted for age, the non-5ARI group had a significantly lower likelihood of PCa detection (hazard ratio [HR], 0.854; $p<0.001$) and radical prostatectomy, including robot-assisted procedures (HR, 0.834, $p<0.001$). The mean number of PSA tests was about 2 times higher in the 5ARI group than in the non-5ARI group (3.98 vs. 2.18, $p<0.001$). Among the subjects who took 5ARIs, the incidence of PCa increased up to 3 years of administration, followed by a decreasing trend thereafter ($p<0.001$).

Conclusions: From this observational study in a country with limited PSA testing uptake, the prescription of 5ARIs, for which repeated PSA testing is encouraged to select suitable patients, enhances the detection of PCa, but does not prevent its development.

Key Words: Prostate cancer, 5-Alpha reductase inhibitor, Prostate-specific antigen

INTRODUCTION

Because of the relatively long latency period of prostate cancer (PCa) and treatment-related morbidity in its management of PCa, the utilization of 5-alpha reductase inhibitors (5ARIs) as a chemo-preventive strategy has been highlighted [1]. This strategy was hypothesized to prevent PCa by decreasing intraprostatic dihydrotestosterone levels. Two large, randomized, placebo-controlled cancer prevention trials were initiated to evaluate the effects of

5ARIs: the Prostate Cancer Prevention Trial (PCPT) for finasteride and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial for dutasteride. Both trials, which were published in the 2000s, demonstrated a similar impact on the risk of PCa development. In the PCPT study, 7 years of finasteride therapy reduced the prevalence of PCa by 24.8% [2]. In the REDUCE trial, dutasteride treatment was associated with a relative risk reduction of 22.8% over 4 years [3], despite the observation of a potentially increased risk of high-grade disease.

Meanwhile, prescriptions of 5ARIs also increased dramatically in Korea, predominantly triggered by the exploding incidence of lower urinary tract symptoms (LUTS), which generally originate from concomitant benign prostate hyperplasia (BPH) along with the extended lifespan. Given the low uptake of prostate-specific antigen (PSA) testing among Korean men (3.1% in 2007 and 7.3% in 2016 among men aged over 40 years [4]) due to the limited social awareness of PCa combined with the lack of a public screening policy [5], the prescription of 5ARIs, for which PSA testing is encouraged to select suitable patients, may promote the identification of PCa by providing repeated opportunities to check men's serum PSA levels. With this background, the purpose of this study was to investigate the influence of 5-ARI prescriptions on the detection of PCa utilizing nationwide data during a recent decade.

MATERIALS AND METHODS

1. Data Source and Study Population

Data were obtained from the National Health Insurance Sharing Service (NHISS). In Korea, national health insurance covers most of its population (98%) and provides universal health coverage. The NHISS database offers most medical data, including diagnostic codes, procedures, prescription drugs, and sequelae, including death.

Men aged over 40 years who underwent PSA testing from 2006 through 2017 were identified from the NHISS database and selected for this study. The PSA test codes utilized in this study were B5490, C4280, and C7428. The code for finasteride (5 mg) and dutasteride (0.5 mg) were 159001ATB and 458801ACS, respectively. Patients newly diagnosed with PCa and registered in the NHISS with an International Classification of Diseases, 10th revision code of C61 or V193/194 each year during the study period were also investigated. Radical prostatectomy, including open and laparoscopic approaches, was identified using reimbursement codes (R3950 and R3960). Robot-assisted radical prostatectomy, which the NHISS did not reimburse, was operationally defined as the absence of a surgery code despite the presence of a general anesthesia code (L1211) and a postoperative pathologic examination code (C5500, C5504, C5505, C5508, C5918, or C5919). Radiation therapy included all radiation modalities, including conformal and intensity-modulated radiation.

All personal identification numbers were encrypted before data processing to comply with the privacy guidelines of the Health Insurance Portability and Accountability Act. The Institutional Review Board of Yeungnam University Hospital investigated and approved this study (approval number: YUMC-2019-11-012-002).

2. Study Design

The subjects were divided into 2 groups: the 5ARI group, which was prescribed two kinds of 5ARIs (including 126 generics for finasteride [5 mg] and 44 generics for dutasteride [0.5 mg]), and their non-5ARI counterparts. For prescriptions of 5ARIs, clinical guidelines have strongly recommended selecting suitable patients using the proper criteria, including the baseline PSA level (recommended when the initial PSA level is over 1.4 ng/mL) and prostate volume (recommended when the prostate is over 40 mL). In the mid-1990s to early 2000s, 5ARIs were introduced into Korea in mid-1990 to early 2000s (the Korea Food and Drug Administration allowed finasteride in 1995 and dutasteride in 2004). Urologists prescribed the majority of 5ARIs during the study period. The reduction of baseline PSA levels after long-term 5ARI administration (over 6 months) has been noticed repeatedly, raising concerns about missing the detection of masked PCa.

The epidemiological characteristics and PCa incidence between the 5ARI and non-5ARI groups were then compared. The number of repetitions of PSA tests was investigated, excluding the number of PSA tests after registration as a

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patient with PCa in the NHISS data. Because registration in the NHISS is mandatory for the official prescription of medications in Korea, the male population over 40 was obtained from the Statistics Korea website. The rates of PSA testing and the incidence of PCa were calculated.

The primary endpoints were (1) the incidence of PCa compared between groups and (2) the rate of PSA testing. The secondary endpoint was the change in PCa incidence over 10 years after 5ARI prescriptions. For patients who were registered as having PCa, the number of PSA tests was limited to tests carried out 3 months before registration in the NHISS, with the removal of all PSA tests after the code of C61 had been assigned for each person.

3. Statistical Analysis

To remove the impact of accumulated data from patients in the previous year before the study period and unfinalized data collection from the insurance surveillance system for patients in the last year, the data from 2006 and 2017 were removed for the final analysis. The chi-square test was used for binary and categorical variables. Since the large number of patients enrolled from the nationwide data tended to have a different age distribution, a multivariable Cox regression test adjusted for age was utilized to compare the 2 groups. The cancer incidence rates were calculated per 1,000 person-years. The Cochran-Armitage trend test was used to investigate PCa trends between the 5ARI and non-5ARI groups and assess the association of variables between these 2 categories. For all comparisons, statistical significance was accepted for p-values <0.05. All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

1. The Relationship Between the Administration of 5ARIs and the Detection of PCa

Across the research period of a decade (2007–2016), 1,528,128 men who were prescribed 5ARIs for a mean of 1.523±2.221 years were identified. Meanwhile, 138,614 patients with PCa were identified, of whom 68,529 (49.4%) were prescribed 5ARIs, with the other 70,085 subjects constituting the non-5ARI group. The finally analyzed data are summarized in Table 1. Among 312,888 men aged over 40 years who received PSA testing in 2007, 73.4% (n=229,760) were prescribed 5ARIs. As the PSA testing rate increased, the proportion of patients who were prescribed 5ARI decreased (58.8% in 2016). The incidence of PCa was significantly higher in the 5ARI group than in the non-5ARI group during all study years (p<0.001), except in 2007, when the rate of PSA testing was the lowest (3.12% among Korean men aged over 40 years). The mean number of repetitions of PSA testing for the study period was significantly higher in the 5ARI group than in the non-5ARI group (3.98 vs. 2.18, p<0.001).

Table 1. The characteristics of the patients enrolled

Year	Middle-aged male population (≥40 yr)				PSA-tested male population (≥40 yr)						
	Total	Registered PCa	Incidence of PSA test (%)	Incidence of PCa (%)	Total	5ARI group	PCa among 5ARI group	PCa incidence among 5ARI group (%)	PCa among non-5ARI group	PCa incidence among non-5ARI group (%)	p-value†
2007	9,999,912	5,292	3.12	0.052	312,888	229,760	3,272	1.42	2,020	2.42	<0.001
2008	10,337,914	6,471	4.63	0.062	479,046	274,835	3,983	1.44	2,488	1.21	<0.001
2009	10,694,580	7,351	5.34	0.068	571,643	331,232	4,557	1.37	2,794	1.16	<0.001
2010	11,039,633	7,848	5.71	0.071	631,417	365,978	5,092	1.39	2,756	1.03	<0.001
2011	11,386,232	8,952	6.14	0.078	700,040	394,019	5,484	1.39	3,468	1.13	<0.001
2012	11,723,878	9,258	6.44	0.078	755,372	420,822	5,892	1.40	3,366	1.01	<0.001
2013	12,042,751	9,515	6.65	0.079	801,241	457,559	6,483	1.41	3,032	0.88	<0.001
2014	12,354,915	9,785	6.72	0.079	831,495	481,797	6,743	1.39	3,042	0.86	<0.001
2015	12,635,426	10,212	6.83	0.080	863,782	505,933	6,682	1.32	3,530	0.98	<0.001
2016	12,886,340	11,800	7.28	0.091	937,548	551,099	7,707	1.39	4,093	1.05	<0.001

PSA, prostate-specific antigen; PCa, prostate cancer; 5ARI, 5-alpha reductase inhibitor.
†p-value for PCa incidence among 5ARI and non-5ARI groups.

2. The Impact of 5ARIs on the Management of PCa

The outcomes of the Cox proportional hazard model adjusted for age are summarized in Table 2. The non-5ARI group had significantly lower likelihoods of cancer detection (hazard ratio [HR], 0.854; p<0.001) and radical surgery, including robot-assisted procedures (HR, 0.834; p<0.001). In contrast, the non-5ARI group had a significantly higher likelihood of radiation therapy (HR, 1.716; p<0.001) and a higher risk of mortality (HR, 1.96; p<0.001) than the 5ARI group. In the 5ARI group, the incidence of PCa increased for 3 years of administration, followed by a subsequent decreasing trend (Cochran-Armitage trend test, p<0.001) (Fig. 1).

DISCUSSION

Although the benefits of PSA-based mass screening policies have remained a matter of debate since 2012 [6-8], serum PSA testing still plays a pivotal role in detecting PCa. Most early-phase PCa cases do not manifest specific symptoms other than ambiguous LUTS, which more frequently originate from concomitant BPH. Indeed, most PCa cases are detected in the non-metastatic stage in Korea [9]. Therefore, the circumstances in which PSA testing is performed provide opportunities to catch PCa in an earlier phase.

Unlike the United States or Europe, which have a long history of clinical applications, ready access to PSA testing, and greater social awareness of PCa, the incidence of PCa in most Asian countries has soared in very recent years. For example, PCa was a relatively less prevalent cancer in Korea until the end of the 20th century. In 2000, PCa became Korean men's 10th most common malignant disease [9]. However, since 2002, when PCa was first reported to be the fifth most common malignant disease among Korean men, its incidence has consistently increased. In 2016, PCa became the fourth most common incident malignancy in men. In the most recent report (2020), it became the third-most common cancer in men and the second-most common among men over 65 years old.

However, this rapidly increasing incidence of PCa was not accompanied by an enhanced public awareness of the disease and its screening strategies. Indeed, in a general survey of 600 members of the Korean population in 2019, only 9.7% of men aged over 40 years were aware of PSA testing, and 83.3% of them had never received PCa screening [5]. Currently, PSA testing is not included in regular check-ups in Korea, which contrasts with the inclusion of tests for other common malignant diseases in men, such as lung, stomach, colon, and liver cancer, which were the first, second, third, and fifth most prevalent malignant diseases among Korean men in 2019 [9]. The nationwide rate of PSA testing during the recent 10-year period (2006–2016), therefore, remained low in Korean men older than 40 years. Although it reached 7.2% in 2016, that figure is still less than a quarter of that reported in the United States [4]. From 2008 to 2016, only around a

Table 2. Summary of the Cox proportional-hazards model adjusted for age

Variable	HR	95% CI	p-value
The detection of PCa			
5ARI group	1 (reference)		
Non-5ARI group	0.854	0.841–0.867	<0.001
The incidence of radical prostatectomy (including robot-assisted procedure)			
5ARI group	1 (reference)		
Non-5ARI group	0.834	0.814–0.855	<0.001
The incidence of radiation therapy for PCa			
5ARI group	1		
Non-5ARI group	1.716	1.694–1.738	<0.001
Overall mortality			
5ARI group	1		
Non-5ARI group	1.96	1.949–1.971	<0.001

HR, hazard ratio; CI, confidence interval; PCa, prostate cancer; 5ARI, 5-alpha reductase inhibitor.

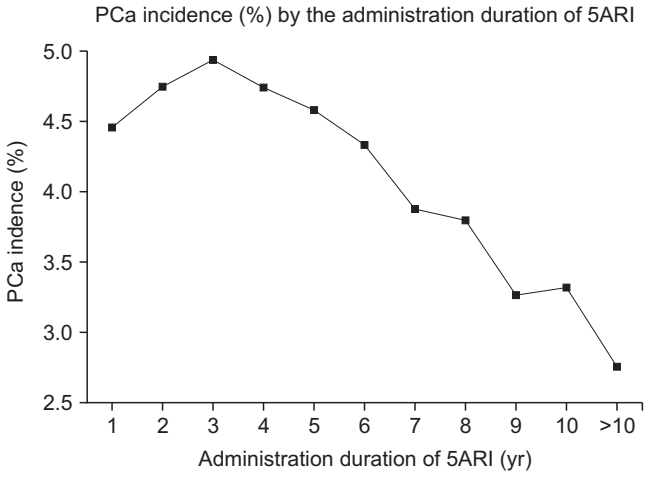

Fig. 1. The incidence of prostate cancer according to the duration of 5-alpha reductase inhibitor (5ARI) administration. PCa, prostate cancer.

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quarter of men with PCa in Korea underwent repeat PSA testing before a pathologic cancer diagnosis was confirmed [10].

The outcomes of this observational study also show how the limited social perception of PSA testing negatively affects PCa detection. In contrast to the well-known randomized controlled trials (RCTs) that were published approximately 2 decades ago, which consistently reported that 5ARIs reduced the development of PCa by 23%–25% [2, 3], the detection of PCa among individuals who were prescribed 5ARIs was instead significantly higher, by about 15%, in this study. Considering the limited opportunities for PSA testing among Korean men during the study period in the absence of a social screening policy and a low social perception of PCa, the prescription of 5ARIs may provide additional opportunities for exposure to PSA testing. In 2007, 73% of nationwide PSA testing was associated with receiving 5ARIs according to this study. In the same year, only 3.12% of men aged 40 received PSA testing [4]. During the study decade, the subjects with 5ARIs had almost twice as high an average number of repeated PSA tests than their non-5ARI counterparts (3.98 vs. 2.18, p<0.001).

Another interesting aspect of this study was that the non-5ARI group had almost twice the overall mortality of the 5ARI group (HR, 1.96; p<0.001), even after adjusting for age. Because the current Korean NHISS does not provide detailed oncologic data, including tumor stage and grade, a direct comparison of tumor aggressiveness between groups was not possible. However, inferences can be made from the data for radiation therapy, which tends to be selected and carried out for patients with advanced stages of disease. Specifically, the fact that PCa patients without previous 5ARI administration had a significantly higher likelihood of radiation therapy implies the more aggressive nature of PCa detected in the non-5ARI group, suggesting possible benefits from earlier cancer detection through more frequent PSA testing. This finding is also inconsistent with those of previous RCTs on 5ARIs, which reported the development of high-grade cancer in patients who received longer-term administration of 5ARIs [11, 12].

If the administration of 5ARIs provokes the biological tumorigenesis of PCa, then a higher incidence of PCa would be observed in subjects with a longer duration of 5ARI administration. With data covering a decade, we could trace the impact of PCa detection among the patients who were prescribed 5ARIs. As shown in Fig. 1, the development of PCa was significantly prevented by the prolonged administration of 5ARIs, especially 3 years after the initial induction and beyond. This observation matches the protective effects of 5ARIs reported in the long-term outcomes of the PCPT and REDUCE trials. At the 16-year follow-up point, Unger et al. [13] reported that men treated with finasteride had a 21.1% lower risk of PCa compared with placebo. Using a registry in Sweden, Wallerstedt et al. [14] evaluated 23,442 men exposed to finasteride or dutasteride for any length of time during an 8-year study period. Treatment with 5ARIs reduced the overall risk of developing PCa, and the effect was more prominent with more prolonged drug exposure (HR, 0.81 for 0.1–2 years vs. HR, 0.31 for 6–8 years).

The authors are well aware of the limitations of this study. First, we could not differentiate significant disease from indolent PCa based on the limited structure of the NHISS. Most RCTs on the efficacy of PSA testing have consistently focused on detecting significant cancer because of the need to consider concerns regarding the overdiagnosis and overtreatment of insignificant PCa. Furthermore, the current version of the NHISS does not contain information on cancer-specific survival, including PCa. Thus, this study could not assess the cost-effectiveness aspect of repeated PSA testing, which was enhanced by the administration of 5ARIs. Second, because the NHISS data did not contain PSA information from private, non-insurance-covered health check-ups, some of those included in the analysis as nonscreened may have been adequately tested. However, given the current reported average retirement age of 51.2 years, according to the most recent employment data among Korean men in 2021 [15], the omission of private PSA testing data likely had a limited impact on the outcomes of this study, since about 90% of the registered PCa cases in Korea are in people older than 60. Furthermore, the reported disparities in PSA testing among Korean men with different socioeconomic statuses should be considered [16]. Third, this observational study design could not identify causal relationships. The advanced age in the 5ARI group may have resulted in the higher detection of PCa than in their

non-5ARI-taking counterparts. Nonetheless, the outcomes from this study, showing that the prescription of 5ARI paradoxically increased the detection of PCa, support the need for expanding a PSA testing-based screening strategy against PCa, balancing the enhanced detection of PCa with cost-effectiveness in prolonging the expected lifespan, given an asymptomatic nature of PCa until its progression into metastatic disease.

CONCLUSIONS

According to this observational study in a country with limited uptake of PSA testing, the prescription of 5ARIs, which encourages repeated PSA testing to select suitable patients, enhanced the detection of PCa more than in their non-5ARI-taking counterparts. With prolonged 5ARI administration, the incidence of PCa increased for 3 years, followed by a continuous decrease thereafter.

NOTES

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