

RESEARCH ARTICLE

Korean Prostate Cancer Patients Have Worse Disease Characteristics than their American Counterparts

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Abstract

Background: Although the PSA test has been used in Korea for over 20 years, the incidence of prostate cancer has risen, and the associated mortality has increased about 13-fold over the 20-year period. Also, several investigators have suggested that Asians in America are more likely to present with more advanced prostate cancer than Caucasians. We compared the characteristics of native Koreans and Americans (Caucasians and African-Americans) undergoing radical prostatectomies in Korea and the US. **Materials and Methods:** Study subjects comprised patients at Korean and US hospitals from 2004 to 2012 who had undergone radical prostatectomies. We compared the characteristics of the subjects, including age, preoperative prostate-specific antigen (PSA) levels, body mass index (BMI), Gleason score, and pathological T stage. **Results:** In total, 1,159 males (502 Koreans, 657 Americans) were included. The Korean and American patients had mean ages of 67.1±6.6 and 59.2±6.7 years, respectively. The mean preoperative PSAs were 15.4±17.9 and 6.2±4.6 ng/mL ($p=0.0001$) and the mean BMIs were 23.6±2.6 and 28.7±4.4 kg/m² ($p=0.0001$), respectively. Pathological localized prostate cancer represented 71.7% of cases for Koreans and 77.6% for Americans ($p=0.07$). According to age, Koreans had higher T stages than Americans in their 50s ($p=0.021$) and higher Gleason scores than Americans in all age groups. According to PSA, Koreans had higher Gleason scores than Americans for PSA >10 ng/mL ($p<0.05$). According to prostate size and Gleason scores, Koreans had higher PSA values than Americans ($p<0.01$). **Conclusions:** These results show that Korean patients have elevated risk of malignant prostate cancers, as indicated by the significantly higher Gleason scores and PSAs, suggesting a need for novel prostate cancer treatment strategies in Korea.

Keywords: Prostatic neoplasm - neoplasm grading - prostate-specific antigen - risk - race.

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Introduction

Prostate cancer is the most common malignancy and the second leading cause of cancer mortality in Western countries. Also, today, the incidence of prostate cancer in Asian populations, included Korea, is increasing rapidly (Center et al., 2012; Jung et al., 2012a).

The incidence of prostate cancer in Koreans is lower than in that Western countries (Center et al., 2012). However, the age-standardized incidence rate of prostate cancer in males, which was 8.4 per 100,000 in 1999, reached 24.8 per 100,000 in 2009 (Jung et al., 2012a). The annual percentage change in prostate cancer was 13.4%, the second largest increase after thyroid cancer. According to the National Cancer Control Institute in Korea, the estimated age-standardized incidence rate was 32.5 per 100,000 in 2012 (Jung et al., 2012b). Prostate cancer was the fourth most common cancer in males of age 65 years and older in 2009 (Jung et al., 2012a).

Furthermore, several investigators have stated that

the aggressiveness of prostate cancer in Asians in North America is more advanced than that of Caucasians and African-Americans at the time of diagnosis. This may depend on geographic, dietary, environmental, and genetic factors.

We compared the characteristics of native Koreans and Americans (Caucasians and African-Americans) who underwent radical prostatectomies in Korea and the US.

Materials and Methods

Study population

All prostate cancer patients registered in three cancer centers (two Korean medical centers: Inje University Paik Hospital, Busan, and Pusan National University Hospital, Busan, and one US medical center: Rutgers Cancer Institute of New Jersey, New Brunswick, NJ) prostate cancer databases from 2004 to 2012 were considered. The study subjects comprised patients at the Korean and US hospitals from 2004 to 2012 who had undergone a radical

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prostatectomy.

The collection and analysis of all data were approved by the Institutional Review Boards of Inje University Paik Hospital, Pusan National University Hospital, and the Cancer Institute of New Jersey. Both Caucasian and African-Americans were included.

We respectively reviewed radical prostatectomy data and compared characteristics including age, preoperative prostate-specific antigen (PSA) levels, prostate-specific antigen density (PSAD), body mass index (BMI), Gleason score, and pathological T stage. BMI was classified by the Steering Committee of the Regional Office for the Western Pacific Region of WHO (WPRO) criteria (Anuurad et al., 2003).

Statistical analysis

The SPSS software (ver. 18) was used for all analyses. Demographic, clinical, and pathological characteristics were examined. Data were presented as means and standard deviation. Clinical variables, such as age, PSA, BMI, and prostate size, in both groups were compared using Student's t-test and categorical variables were compared using chi-squared tests and Fisher's exact test.

Univariate and multivariate linear regression analyses were used to examine the predictive value of the clinicopathological features for preoperative PSA level. p values of <0.05 were considered to indicate statistical significance.

Results

The clinical and pathological characteristics of the prostate cancer patients in the two countries are summarized in Table 1. Of the 1,159 cases, 507 (43.7%) were Koreans and 657 (56.3%) were Americans.

At diagnosis, there was a significant difference in mean age (67.1±6.6 years in Koreans vs 59.2±6.7 years in Americans; p=0.0001). The mean preoperative PSA level was higher in Koreans (15.4±17.9 ng/mL for Koreans vs. 6.2±4.6 ng/mL for Americans). The prostate of Koreans was smaller than that of Americans (p=0.0001; Table 1). Although there was no difference in pathological T

Table 1. Overall Characteristics

	Koreans n=502	Americans n=657	p value
Age, mean±SD	67.1±6.6	59.2±6.7	0.0001
BMI*, mean±SD	23.6±2.6	28.7±4.4	0.0001
Normal (<23)	198 (39.4)	43 (6.5)	
Overweight (23≤25)	174 (34.7)	73 (11.1)	
Obese (≥25)	130 (25.9)	541 (82.3)	
prePSA, mean±SD	15.4±17.9	6.2±4.6	0.0001
PSAD, mean±SD	0.45±0.61	0.13±0.1	0.0001
Prostate size, mean±SD	40.2±20.5	47.9±18.3	0.0001
Pathological Gleason score			0.0001
≤6	166 (33.1)	291 (44.3)	
7	268 (53.4)	278 (42.3)	
≥8	68 (13.5)	88 (13.4)	
Pathological T stage			0.07
pT2	360 (71.7)	510 (77.6)	
pT3	141 (28.1)	146 (22.2)	
pT4	1 (0.2)	1 (0.2)	

*WPRO (2000): The Steering Committee of the Regional Office for the Western Pacific Region of WHO, International Association for the Study of Obesity and the International Obesity Task Force proposed an appropriate classification of obesity in Asia in 2000

stage, the overall pathological Gleason score was higher in Koreans (p=0.0001).

Next, we analyzed the characteristics of the prostate cancer according to age, preoperative PSA levels, and BMI in both groups. According to age, Korean in their 50s had more advanced-stage cancers than Americans (p=0.021). In particular, Korean had more aggressive Gleason scores in those under 70 years old, while Americans had higher Gleason score in those over 71 years old (Table 2). While prostate cancer in Koreans occurring in males older than 60 accounted for 84.5% (424/507), 84.9% (558/657) of the Americans were between 50 and 70 years old (Table 2).

According to preoperative PSA levels, there was no difference in terms of Gleason score between the two groups below 10 ng/mL (p>0.05). Koreans had higher Gleason scores than Americans with a PSA above 10 ng/mL (p<0.05; Table 3). According to preoperative PSA levels, there was no difference in pathological T stage between the groups.

According to BMI, there was no difference in terms of Gleason score or pathological stage between the groups (Table 4).

Table 2. Comparison of Pathological T Stage According to age (A) and Comparison of Gleason Score According to age (B)

		Koreans N=502	Americans N=657	p value
(A) Comparison of pathological T stage according to age				
≤50 years	pT2	1 (25.0)	52 (73.2)	0.098
	pT3	3 (75.0)	18 (25.4)	
	pT4	0 (0)	1 (1.4)	
	Subtotal	4	71	
50< ≤60 years	pT2	53 (71.6)	249 (82.5)	0.021
	pT3	20 (27.0)	53 (17.5)	
	pT4	1 (1.4)	0 (0)	
	Subtotal	74	302	
60< ≤70 years	pT2	196 (72.3)	193 (75.4)	0.43*
	pT3	75 (27.7)	63 (24.6)	
	pT4	0 (0)	0 (0)	
	Subtotal	271	256	
>71 years	pT2	110 (71.9)	16 (57.1)	0.124*
	pT3	43 (28.1)	12 (42.9)	
	pT4	0 (0)	0 (0)	
	Subtotal	153	28	
(B) Comparison of Gleason score according to age				
≤50 years	≤6	1 (25.0)	39 (54.9)	0.016
	7	1 (25.0)	27 (38.0)	
	≥8	2 (50.0)	5 (7.0)	
	Subtotal	4	71	
51≤60 years	≤6	17 (23.0)	144 (47.7)	0.0001
	7	44 (59.5)	130 (43.0)	
	≥8	13 (17.6)	28 (9.3)	
	Subtotal	74	302	
61≤70 years	≤6	87 (32.1)	105 (41.0)	0.008
	7	150 (55.4)	107 (41.8)	
	≥8	34 (12.5)	44 (17.2)	
	Subtotal	271	256	
>71 years	≤6	61 (39.9)	3 (10.7)	0.0001
	7	73 (47.7)	14 (50.0)	
	≥8	19 (12.4)	11 (39.9)	
	Subtotal	153	28	

We also analyzed PSA according to Gleason score and prostate size between the groups. PSA levels in Korean were elevated with increasing prostate size and Gleason score compared with those of Americans (Table 5).

We then compared Gleason score and preoperative PSA level according to pathological T stage in the two groups (Table 6). In pT2, Koreans had unfavorable Gleason scores; at identical Gleason scores, Koreans had higher PSA levels than Americans ($p < 0.001$). In patients with pT3 and above, there was a significant difference between Koreans and Americans in terms of Gleason

Table 3. Comparison of Gleason Score According to Preoperative PSA Levels (A) and Comparison of Pathological T Stage According to Preoperative PSA Levels (B)

		Koreans N=502	Americans N=657	p value
(A) Comparison of Gleason score according to preoperative PSA levels				
PSA \leq 4	\leq 6	18 (52.9)	91 (60.7)	0.532
	7	13 (38.2)	52 (34.7)	
	\geq 8	3 (8.8)	7 (4.7)	
	Subtotal	34	150	
4<PSA \leq 10	\leq 6	101 (43.3)	181 (40.8)	0.2
	7	111 (47.6)	202 (45.5)	
	\geq 8	21 (9.0)	61 (13.7)	
	Subtotal	233	444	
10<PSA \leq 20	\leq 6	32 (23.2)	17 (32.7)	0.041
	7	86 (62.3)	22 (42.3)	
	\geq 8	20 (14.5)	13 (25.0)	
	Subtotal	138	52	
PSA>20	\leq 6	15 (15.5)	2 (18.2)	0.016
	7	58 (59.8)	2 (18.2)	
	\geq 8	24 (24.7)	7 (63.3)	
	Subtotal	97	11	
(B) Comparison of pathological T stage according to preoperative PSA levels				
PSA \leq 4	pT2	29 (85.3)	131 (87.3)	0.75
	pT3	5 (14.7)	19 (12.7)	
	pT4	0 (0.0)	0 (0.0)	
	Subtotal	34	150	
4<PSA \leq 10	pT2	192 (82.4)	340 (76.6)	0.173
	pT3	40 (17.2)	103 (23.2)	
	pT4	1 (0.4)	1 (0.2)	
	Subtotal	233	444	
10<PSA \leq 20	pT2	101 (73.2)	34 (65.4)	0.289
	pT3	37 (26.8)	18 (34.6)	
	pT4	0 (0.0)	0 (0.0)	
	Subtotal	138	52	
PSA>20	pT2	38 (39.2)	5 (45.5)	0.751
	pT3	59 (60.8)	6 (54.5)	
	pT4	0 (0.0)	0 (0.0)	
	Subtotal	97	11	

Table 4. Comparison of Gleason Score According to Body Mass Index (BMI) (A) and Comparison of Pathological T Stage According to BMI (B)

		Koreans N=502	Americans N=657	p value
(A) Comparison of Gleason score according to BMI				
BMI normal (<23)	\leq 6	57 (28.8)	18 (41.9)	0.222
	7	113 (57.1)	19 (44.2)	
	\geq 8	28 (14.1)	6 (14.0)	
	Subtotal	198	43	
BMI overweight (23 \leq <25)	\leq 6	66 (37.9)	35 (47.9)	0.334
	7	86 (49.4)	31 (42.5)	
	\geq 8	22 (12.6)	7 (9.6)	
	Subtotal	174	73	
BMI obese (\geq 25)	\leq 6	43 (33.1)	238 (44.0)	0.055
	7	69 (53.1)	228 (42.1)	
	\geq 8	18 (13.8)	75 (13.9)	
	Subtotal	130	541	
(B) Comparison of pathological T stage according to BMI				
BMI normal (<23)	pT2	136 (68.7)	37 (86.0)	0.7
	pT3	61 (30.8)	6 (14.0)	
	pT4	1 (0.5)	0 (0.0)	
	Subtotal	198	43	
BMI overweight (23 \leq <25)	pT2	120 (69.0)	55 (75.3)	0.359*
	pT3	54 (31.0)	18 (24.7)	
	pT4	0 (0.0)	0 (0.0)	
	Subtotal	174	73	
BMI obese (\geq 25)	pT2	104 (80.0)	418 (77.3)	0.722
	pT3	26 (20.0)	122 (22.6)	
	pT4	0 (0.0)	1 (0.2)	
	Subtotal	130	541	

*Fisher's exact test

Table 5. Comparison of Gleason Score and Prostate size According to Preoperative PSA Levels

	Koreans N=502	Americans N=657	p value
Prostate size			
\leq 25 g	15.81 \pm 20.98	5.35 \pm 2.75	0.01
25< \leq 40 g	15.67 \pm 17.14	5.55 \pm 3.6	
>40 g	14.77 \pm 17.76	6.59 \pm 5.12	
Gleason Score			
Gleason score \leq 6	9.38 \pm 7.93	5.52 \pm 3.26	0.001
Gleason score =7	17.11 \pm 19.94	6.01 \pm 3.07	
Gleason score \geq 8	23.16 \pm 22.53	9.41 \pm 9.11	

Table 6. Comparison of Gleason Scores and Preoperative PSA Levels according to Pathological T Stage

	Gleason score		p value*	PSA		p value
	Koreans	Americans		Koreans	Americans	
pT2:						
GS \leq 6	146 (40.6)	255 (50.0)	0.007	8.5 \pm 6.0	5.5 \pm 3.4	0.0001
GS \geq 7	214 (59.4)	255 (50.0)		13.9 \pm 15.5	6.0 \pm 3.3	0.0001
pT3, T4:						
GS \leq 6	20 (14.1)	36 (24.5)	0.027	16.0 \pm 14.6	5.6 \pm 2.5	0.0001
GS \geq 7	122 (85.9)	111 (75.5)		26.1 \pm 25.6	8.7 \pm 8.2	0.0001

*Fisher's exact test

Table 7. Univariate/Multivariate Analysis of Preoperative PSA according to Clinicopathological Factors

	Univariate analysis			Multivariate analysis		
	Standardized coefficient β	p value	95%CI	Standardized coefficient β	p value	95%CI
Residence place (America/Korea)	0.345	0.001	7.693-10.588	0.32	0.001	6.641-10.288
Age	0.19	0.001	0.225-0.417	0.01	0.754	-0.086-0.119
BMI	-0.193	0.001	-0.722-(-0.394)	-0.011	0.728	-0.214-0.150
Prostate size	-0.015	0.616	-0.048-0.029			
Gleason score	0.226	0.001	2.688-4.467	0.151	0.001	1.524-3.26
T stage	0.238	0.001	2.285-3.688	0.182	0.001	1.592-2.961

*Adjusted R²=0.192

scores and PSA levels (Table 6).

On univariate analysis, the following five variables were significant factors for high PSA levels: residence (American vs Korean), age, BMI, Gleason score, and pathological T stage. However, on multivariate linear regression analysis, place of residence (American vs Korean), Gleason score, and pathological T stage remained strong and independent factors for elevated PSA; place of residence was a strong factor (Table 7).

Discussion

The present study showed that Koreans with localized or locally advanced prostate cancer had poorer characteristics than similar Americans. In particular, Korean prostate cancer patients between 50 and 60 years old had higher Gleason scores and higher T stages than Americans.

The PSA test for the diagnosis of prostate cancer has been used in Korea for 20 years. Although its value as a screening test is controversial (Ilic et al., 2013), the PSA test is widely used in many countries, including Korea and the US. Since the PSA testing era began, the incidence of prostate cancer in Asian populations, including Korea, has been found to be lower than that in Western countries (Center et al., 2012). However, the average annual percentage change (AAPC) in Asia over the last 10 years has been high; indeed, the AAPC in Korea was 13.8 between 1999 and 2007, which is the most rapid increase globally (Center et al., 2012).

Today, the risk factors for prostate cancer are believed to include advanced age, genetic variation, race, geographic variation, and diet (Center et al., 2012; Pan et al., 2012; Tabung et al., 2012; Wood et al., 2012). Several studies have shown differences in prostate cancer according to race in terms of incidence, pathological differentiation, and outcomes. A study of the geographic variation in prostate cancer incidence in 40 countries showed that North America, and western and northern Europe had the highest prostate cancer incidence and that the incidence in Asia was among the lowest between 2000 and 2006 (Center et al., 2012). An investigation in the US analyzed the prostate cancer characteristics of 8,840 Asians in California between 1995 and 2004 (Robbins et al., 2007). Though the Korean population comprised only a small proportion of this (0.03%), the incidence of prostate cancer in the US increased gradually over a 10-year period. For a similar period (1999-2009), the age-standardized cancer incidence of prostate cancer in Korea increased markedly from 8.4 to 24.8 per 100,000 (Jung et al. 2012a). Indeed, the annual percentage increase is second only to that of thyroid cancer.

Several studies have reported that Asians resident in North America have more aggressive cancers compared with Caucasians or African-Americans (Lin et al., 2002; Robbins et al., 2007). Robbins et al. reported that the proportion of white residents with poorly differentiated histological grade (Gleason score 8-10) was 22.9%, while those of Koreans, Chinese, and Japanese males in California were 34.5%, 30.9%, and 28.6%, respectively (Robbins et al., 2007). Furthermore, the proportion

of poorly differentiated cancers, Gleason scores, and advanced stage in Koreans was the highest among the Asians examined. In this study, the proportion with a Gleason score ≥ 7 was higher in Koreans (66.9%) than Americans (55.7%). Most notably, Koreans younger than 70 years and with PSA >10 ng/mL showed considerably higher risk of more unfavorable Gleason scores than Americans in this study (Tables 3, 5). Also, in the same Gleason score group, preoperative PSA levels in Koreans were higher than in Americans, by 1.7-2.5 fold (mean PSA levels; see Table 6). Kim et al. reported changes in Gleason Score in prostate cancer over the last 12 years in a Korean population (Kim et al., 2012). In total, 2,508 prostate cancer patients undergoing radical prostatectomies were enrolled. Over the 12 years, most of the prostate cancer was poorly differentiated, with Gleason scores of 7-10 (81.8%), although the proportion with a Gleason score of 6 increased slightly, from 15.0-18.2%. Also, the Surveillance, Epidemiology, and End Results (SEER) study data showed that Asian residents in the US had more distant metastases than Caucasians at the time of diagnosis during the period 1988-1994 (Lin et al., 2002).

In contrast to these unfavorable findings, some researchers have reported good results in Asians. Although a small number of Asians (5%) were included, in residents of the eastern US, there was no difference by race in Gleason score, compared with Caucasian and African-Americans (Raymundo et al., 2011). Some investigators have suggested that Asian populations have a good prognosis, rather than poor characteristics (Robbins et al. 2007). In fact, Asians in the US had better survival than other races, including Caucasians, African-Americans, and Hispanics, according to the SEER data (Siegel R et al., 2012). Although the mortality rate for Caucasians was 22.4 per 100,000 population, that for Asians was 10.5 per 100,000 population.

As shown in Table 2, in Americans, older patients tended to present with higher Gleason scores. However, prostate cancer in older Koreans showed consistently lower Gleason scores.

Prostate cancer in Koreans aged 50 years or younger represented a small proportion (0.8%). The proportion in those between 50 and 60 years old was up to 14.7%. Although these data may not be representative of all Korean males, urologists should consider the possibility of prostate cancer in such individuals.

Our study had several limitations. First, we did not review pathological findings centrally. Second, there may have been selection bias, because of the regional nature of the data (Busan in Korea and New Jersey in US) in the two countries. Third, in this study, no prognosis or outcome information after the radical prostatectomies was available for comparison, only tumor nature, because the outcome and prognosis of prostate cancer would be affected by the surgeons' technical skill and operative methods (open, laparoscopic, robotics). Despite these limitations, this is the first head-to-head comparison of prostate cancer in Koreans and Americans during the same period.

In conclusions, this present study shows that the characteristics of prostate cancer in Koreans differ from those in Americans. In particular, Koreans in their 50s

and 60s have worse pathological findings than Americans and more advanced pathological T stages in their 50s. Thus, this study suggests that new treatment strategies, focused on Koreans, may be needed for the management of prostate cancer.

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