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Prostate Cancer Prognostic Factors among Patients Born in the US Compared to Those Born Abroad.

By

Junjun Xu

MPH

Epidemiology

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Michael Goodman, MD, MPH

Faculty Thesis Advisor

Abstract Cover Page

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By

Junjun Xu

B.A., Renmin University of China, 2011

Thesis Advisor: Michael Goodman, MD, MPH

An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology

2013

Prostate Cancer Prognostic Factors among Patients Born in the US Compared to Those Born Abroad.

Abstract

Background: US surveillance data indicate that incidence of prostate cancer differs by place of birth among Asian men. However, it is less clear if the prognostic factors for prostate cancer also differ by place of birth. We examined differences in the measures of disease severity among US-born and foreign-born Asian prostate cancer patients.
Methods: The study included 105,321 prostate cancer patients diagnosed between 2004 and 2009 and reported to the Surveillance Epidemiology and End Results (SEER) program. Logistic regression models were used to evaluate the relation of place of birth to three outcomes: PSA level, Gleason score, and T stage, adjusting for age, marital status, Rural-Urban Continuum Code, and SEER registry. All outcome variables were binary using different cutoffs: ≥4 ng/ml, ≥10 ng/ml and ≥20 ng/ml for PSA; ≥7 and ≥8 for Gleason score; and ≥T2 and ≥T3 for clinical stage.
Results: Elevated PSA was more common among foreign born Asian men regardless of the cutoff used. In the analysis by ethnic group the association with PSA was most pronounced at cut point of ≥20 ng/ml for Chinese men (OR=1.68, 95% CI: 1.02-2.75), and at cut point of ≥4 ng/ml (OR=2.73, 95% CI 1.20-6.21) for Japanese men. A statistically significant association with Gleason score was only found among foreign born Japanese men and only for the cutoff ≥7 (OR=1.71, 95%CI 1.12-2.61). There was no difference in clinical T stage between US-born and foreign-born Asian men. Inclusion of cases with missing place of birth or restriction of data to those who underwent radical prostatectomy did not substantially change the results.
Conclusions: The data suggest that foreign-born Asian prostate cancer cases may have higher PSA levels at diagnosis than their US born counterparts. For other prognostic markers the associations were less consistent and did no form a discernible pattern.

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Introduction

Prostate cancer (PCa) is the most common malignancy among males in the United States.[1] Although the five-year survival among PCa patients with localized disease is close to 100 percent, prostate cancer is still the second leading cause of cancer death among American males.[2]

The incidence and mortality rates of PCa vary markedly worldwide.[3, 4] The highest incidence rates are reported in the United States and New Zealand and the lowest rates are observed in East Asia. The PCa mortality rates are the highest in the Caribbean and the lowest in East Asian countries. US cancer surveillance data indicate that incidence of prostate cancer may differ by place of birth and migrant studies showed a shift toward higher rates following migration to a higher-risk country.[5, 6]

While ethnic, geographic, and place of birth-related differences in PCa incidence and mortality are well documented, it is less clear if the same differences pertain to clinical characteristics of the disease. For example, it is not known if the prognostic factors of men diagnosed with prostate cancer differ by place of birth. The most commonly used prognostic factors for PCa are serum levels of prostate-specific antigen (PSA), Gleason score and clinical stage. Information on all of these factors is now collected as part of population-based cancer surveillance in the United States.

In the mid to late 1980s, PSA testing was introduced in the United States for early detection of prostate cancer and monitoring of disease progression.[7] Although the use

of PSA for screening is a matter of debate,[8, 9] it remains a significant prognostic marker and an independent predictor of PCa treatment outcomes.[10-13]

In 1966, Gleason created a five-level scale system for prostatic adenocarcinoma, which summarized two grade patterns to define the final score.[14] Since then, the Gleason system, which has undergone several modifications, has been repeatedly validated as one of the most critical predictors of prostate cancer prognosis.[15-18] The values of Gleason score typically range between 5 and 10 and the scores of <6, 7, and 8-10 are considered to represent low-, intermediate- and high-grade cancer.[19]

Another measure of PCa prognosis is stage and specifically clinical T-stage. TNM-staging system was developed by the American Joint Committee on Cancer (AJCC) in 1977 to provide a common language for clinicians to report disease extent.[19] Prostate cancer clinical staging, obtained from examinations before treatment, differs from pathologic staging, which is based on sections of tissue and available only for those patients who underwent radical prostatectomy. The clinical stage has been shown to be a predictor of prostate cancer progression and disease-specific death in several studies.[20, 21]

The goal of the present study is to assess the differences in prognostic factors between US- and foreign-born prostate cancer patients diagnosed and treated in the United States. Several previous studies used SEER data to compare incidence and survival of cancer patients by place of birth, however, few were focused on the differences in prognostic factors.[22-24] Surveillance Epidemiology and End Results (SEER),

program, which now includes about 26% of the US population, offers a valuable source of data suitable for studies of prostate cancer. In 2004, SEER clinical and prognostic variables for several cancer sites; for PCa these additional variables included PSA value and Gleason's score.[25] This made it possible to examine the association between birth place and prognostic factors for prostate cancer using SEER data.

To our knowledge only one previous study examined the distributions of PSA, Gleason score and stage in African-American men diagnosed with prostate cancer compared to patients of African descent that were born in other parts of the world.[26] The current study builds on these previous analyses by focusing on patients of Asian race.

Methods

We used SEER data pertaining to cases of malignant prostate cancer diagnosed between 2004 and 2009 (n=342,892). Men of Asian and Oceanian origin were included into a single race category (identified as "Asian" thereafter). Cases whose race/ethnicity were not white or Asian (n=59,697), diagnosed before 18 years old (n=23), and had missing data on covariates (n=274) were excluded. We further removed cases with recorded birth place other than the US or Asia and Oceania (n=12,459). US-born whites were used as reference group for comparison, we did not include cases among whites whose place of birth was missing (n=163,524). Filipino (n=3,925), Chinese (n=3,013) and Japanese (n=2,525) were identified as the most common ethnicity subgroups. Birth place was used as main predictor for statistical analysis. However, 47.5% of all Asian cases were found missing birth place. The percentages of cases with missing place of birth were 49.0%, 46.2% and 37.3% for Chinese, Japanese and Filipino respectively. The previous study of Asians in the Northern California, the great majority of persons with missing birth place data were found to have been born in the US.[27] We therefore performed additional analysis where Asian cases born abroad were compared to all persons that were either documented to have been born in the US or had missing place of birth information.

The primary outcomes were PSA level, Gleason score and T stage. Gleason score and T stage in the SEER data were recorded based on radical prostatectomy (if performed) or needle biopsy (for patients that were treated non-surgically). PSA level was recorded using the highest value before diagnosis or treatment. All three major

outcomes were further classified on a dichotomous scale and sensitivity analyses were conducted at various cut points. The cutoffs for PSA were 4, 10, and 20 ng/ml; Gleason score was analyzed by comparing 8-10 versus 2-7 and 7-10 versus 2-6; and for T stage the cutoff points were T2 and T3.

The primary comparison was between foreign-born and US-born Asians (alone or in combination with those whose birth place was missing). The corresponding comparisons were also used for ethnic subgroups of Chinese, Japanese and Filipino. All analyses were performed using multivariable logistic regression models with results expressed as adjusted odds ratios (OR) and 95% confidence intervals (CI). Age at diagnosis was included in models as a continuous variable. Rural-Urban Continuum (level of urbanization for each subjects county of residence) and marital status (whether married or not) were also included as covariates.

Additional analysis restricted to cases receiving radical prostatectomy to limit Gleason score and T stage data to presumably more accurate pathology-derived information. All statistical analyses were conducted using SAS software (version 9.3; Statistical Institute, Cary, NC, USA).

Results

Among 7,824 Asian prostate cancer patients with known place of birth, most (5,427 or 69%) were born outside the US. Foreign-born patients constituted the majority of cases in all ethnic groups except Japanese among whom only 12% born outside the US. Table 1 summarizes disease and socio-demographic characteristics of study participants. The mean age at diagnosis was 68.5 years among foreign born study subjects and 71.0 years among US-born Asians (P-value<0.0001). The age differences by place of birth were also observed among Chinese (P-value=0.025) and Japanese (P-value<0.0001) patients, but not among Filipinos (P-value=0.2173). The proportion of single men was lower among foreign-born patients in all categories except the Japanese (Table 1).

The distributions of PSA level varied by place of birth for all groups except Filipinos; however these differences in Chinese and Japanese were in opposite directions. Very high levels (≥20 ng/ml) of PSA were more common in foreign born Chinese and less common in Japanese immigrants compared to their respective US-born counterparts. The percentage of cases with advanced Gleason scores (score 8-10) was 20.3% in foreign born Asians, which was statistically significantly lower than 24.1% among Asian men born in the US. These differences were less pronounced in ethnic subgroups and directions of the differences varied by ethnicity. The percentage of advanced T stage (T3 and worse) was 11.2% among all Asian immigrants and ranged from 10.7% in Chinese and Filipinos to 12.5% in Japanese. These proportions were all significantly higher than those in the US-born counterparts.

In the multivariable analyses adjusting for age at diagnosis, marital status, RUC code and SEER registry, Asian men born abroad were more likely to have moderately elevated PSA (≥4 ng/ml) compared to US-born Asians (OR=1.33, 95% CI: 1.07-1.64). This difference was primarily driven by the results for Japanese (OR=2.42; 95% CI: 1.10-5.35) and was not evident in Chinese or Filipinos (Table 2). As the PSA cutoff increased the difference for all Asians persisted, but the results were mostly attributable to the Chinese. The results for Filipinos demonstrated no difference in PSA regardless of the cutoff level. The results of alternative analyses, which included cases with missing birth place into the US-born category were essentially the same (Table 2).

Table 3 shows the results of analyses for Gleason score. Using the Gleason score cut point of ≥8, models limited to cases with documented place of birth showed no difference between US- and foreign born subjects in any of the categories. The results for cut point ≥7 were similar for all except Japanese who demonstrated a significant increase in elevated Gleason score among foreign-born men (OR=1.71; 95% CI: 1.12-2.61). Once the sample was increased to include men with unknown place of birth who were presumed to be US-born the results for the Japanese remained essentially the same. There was, however, evidence that Chinese immigrants were more likely to have higher Gleason scores compared to all other Chinese men with ORs (95% CIs) of 1.26 (1.06-1.49) and 1.33 (1.09-1.62) for cutoffs of ≥7 and ≥8, respectively. Moreover, using Gleason score cutoff of ≥8 the difference between PCa patients born in the Philippines and all other Filipino cases was also statistically significant, which resulted in a significant difference among all Asian cases combined (OR=1.25; 95% CI: 1.13-1.37)

In the analyses for T-stage multivariable models restricted to cases with recorded birth place demonstrated similar ORs among all Asians and in Chinese, Japanese and Filipinos irrespective of the cutoff. Inclusion of men with missing place of birth did not substantially change the point estimates but the 95% CIs became narrower. As a result, statistically significant differences were observed among all Asians (OR=1.26; 95% CI 1.12-1.41) and Chinese men (OR=1.40; 95% CI 1.07-1.83) using stage cutoff of T3 or worse.

Supplementary analyses for Gleason score were used after restricting the data to cases treated with radical prostatectomy. No meaningful differences were observed in those sub-analyses compared to all other results (data not shown). .

Discussion

The primary finding in this study was that foreign born Asian prostate cancer patients were more likely to have elevated PSA than their US born counterparts. Gleason score and T stage were not consistently associated with the place of birth, although some analyses did show statistically significant departures from unity. The inclusion of cases with missing birth place did not substantially change the results. Thus despite known differences in incidence rates among foreign born and US born Asians, the markers of disease severity were comparable.

One possible explanation for the observed association between PSA and place of birth is the lower PSA screening rates in general among foreign born men.[28] Thus, it is possible that immigrants may be more likely to present with symptomatic disease that is characterized by higher PSA. On the other hand, the comparable Gleason scores and T stages across place of birth categories seem to indicate that foreign born immigrants are not more likely to have more advanced disease. An alternative explanation is the immigrant men are less likely to undergo a biopsy in follow up to a given PSA value than men who are US born.

Several limitations of this study warrant cautious interpretation of findings. One major limitation is a large proportion of cases (48%) lacking information on birth place. Among Asian men with missing birth palce, the proportions of those with elevated PSA (≥10 ng/ml, 28%), higher Gleason score (≥8, 16%) or advanced T stage (≥T3, 9%) were lower than the corresponding proportions among those with documented place of birth

(33%, 21% and 11% respectively). Nevertheless, the results were similar with or without inclusion of patients whose birth place information was missing. Another limitation of this study is that only the highest PSA level and one result of Gleason score (from surgery or biopsy, but not both) were available. On the other hand, restriction of the data to patients who underwent radical prostatectomy did not substantially alter the results. While we were able to compare patients born in the US to those born abroad, the duration of residence in the US for foreign-born individuals was not available. Duration of US residence may be associated with access to health care, lifestyle factors and socio-economic status of immigrants. These factors were previously found to be related to disease severity among PCa patients.[29-31]

Despite these limitations, our study offers an interesting insight into the association between place of birth and the disease severity among Asian PCa patients. Our data suggest that foreign-born Asian prostate cancer cases may have higher PSA levels at diagnosis than their US born counterparts. For other prognostic markers the associations were less consistent and did no form a discernible pattern.

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Tables 1. Demographic and clinical characteristics among US-born whites and by place of birth Asian prostate cancer patients, SEER18 2004-2009*

	US-born White	All Asian		Chinese		Japanese		Filipino	
		US-born	Original-born	US-born	Original-born	US-born	Original-born	US-born	Original-born
	(N=90,418) N (%)	(N=2,397) N (%)	(N=5,427) N (%)	(N=268) N (%)	(N=1,270) N (%)	(N=1,193) N (%)	(N=160) N (%)	(N=193) N (%)	(N=2,269) N (%)
Age at diagnosis									
(Mean, SD)	68.3 (9.87)	71.0 (9.51)	68.5 (8.98)	71.4 (9.22)	70.0 (9.21)	73.0 (9.48)	68.0 (9.22)	69.3 (9.03)	68.5 (9.09)
			P<0.0001		P=0.0250		P<0.0001		P=0.2173
Marital Status									
Married	63,058 (69.7)	1,639 (68.4)	4,443 (81.9)	182 (67.9)	1,072 (84.4)	829 (69.5)	115 (71.9)	142 (73.6)	1,843 (81.2)
Single	22,231 (24.6)	528 (22.0)	694 (12.8)	55 (20.5)	140 (11.0)	241 (20.2)	36 (22.5)	37 (19.2)	309 (13.6)
Unknown	5,129 (5.7)	230 (9.6)	290 (5.34)	31 (11.6)	58 (4.6)	123 (10.3)	9 (5.6)	14 (7.3)	117 (5.2)
			P<0.0001		P<0.0001		P<0.0001		P<0.0001
Level of Urbanization									
<100,000	40,343 (44.6)	1,649 (68.8)	823 (15.2)	164 (61.2)	88 (6.93)	860 (72.1)	32 (20.0)	137 (71.0)	458 (20.2)
>=100,000	50,086 (55.4)	748 (31.2)	4,604 (84.8)	104 (38.8)	1,182 (93.1)	333 (27.9)	128 (80.0)	56 (29.0)	1,811 (79.8)
			P<0.0001		P<0.0001		P<0.0001		P<0.0001
PSA									
0-3.9	10,597 (11.7)	186 (7.8)	386 (7.1)	16 (6.0)	83 (6.5)	91 (7.6)	7 (7.4)	16 (8.3)	151 (6.7)
4-9.9	42,427 (46.9)	1,078 (45.0)	2,582 (47.6)	136 (50.8)	605 (47.6)	503 (42.2)	85 (53.1)	78 (40.4)	1,067 (47.0)
10-19.9	11,2879 (12.5)	460 (19.2)	957 (17.6)	49 (18.3)	240 (18.9)	241 (20.2)	32 (20.0)	38 (19.7)	375 (16.5)
≥20	10,721 (11.9)	339 (14.1)	836 (15.4)	29 (10.8)	201 (15.8)	168 (14.1)	18 (11.3)	41 (21.2)	375 (16.5)
Unknown	15,394 (17.0)	334 (13.9)	666 (12.3)	38 (14.2)	141 (11.1)	190 (15.9)	18 (11.3)	20 (10.4)	301 (13.3)
			P<0.0001		P=0.0247		P=0.0003		P=0.1721
Gleason Score									
2-7	65,369 (72.3)	1,601 (66.8)	3,826 (70.5)	193 (72.0)	877 (69.1)	756 (63.4)	112 (70.0)	130 (67.4)	1,579 (69.6)
8-10	14,753 (16.3)	577 (24.1)	1,099 (20.3)	53 (19.8)	279 (22.0)	316 (26.5)	32 (20.0)	46 (23.8)	468 (20.6)
Unknown	10,296 (11.4)	219 (9.1)	502 (9.3)	22 (8.2)	114 (9.0)	121 (10.1)	16 (10.0)	17 (8.8)	222 (9.8)
			P<0.0001		P=0.0765		P<0.0001		P=0.0336*
T Stage									
T0-T2C	74,597 (82.5)	1,971 (82.2)	4,465 (82.3)	226 (84.3)	1,053 (82.9)	974 (81.6)	130 (81.3)	154 (79.8)	1,865 (82.2)
T3+	9,125 (10.1)	241 (10.1)	610 (11.2)	19 (7.1)	136 (10.7)	113 (9.5)	20 (12.5)	20 (10.4)	243 (10.7)
Unknown	6,696 (7.4)	185 (7.7)	352 (6.5)	23 (8.6)	81 (6.4)	106 (8.9)	10 (6.3)	19 (9.8)	161 (7.1)
			P<0.0001		P=0.0253		P=0.0469		P=0.0160

Table 2. Multivariable models predicting PSA level among Asian men diagnosed with prostate cancer, SEER18 2004-2009

	Model 1[a]					
	Sample Size	PSA ≥4		PSA ≥10		PSA ≥20	
		OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI
All Asian	7,824	**1.33***	**(1.07-1.64)**	**1.27***	**(1.12-1.45)**	**1.36***	**(1.15-1.61)**
Chinese	1,538	0.80	(0.42-1.52)	1.32	(0.92-1.89)	**1.68**	**(1.02-2.75)**
Japanese	1,353	**2.73***	**(1.20-6.21)**	1.24	(0.81-1.89)	0.89	(0.50-1.56)
Filipino	2,462	1.28	(0.71-2.31)	1.00	(0.71-1.42)	0.95	(0.63-1.42)
	Model 2[b]						
	Sample Size	PSA ≥4		PSA ≥10		PSA ≥20	
		OR[c]	95% CI	OR	95% CI	OR[c]	95% CI
All Asian	14,903	**1.20***	**(1.05-1.38)**	**1.31***	**(1.21-1.43)**	**1.41***	**(1.27-1.57)**
Chinese	3,013	1.11	(0.82-1.51)	**1.34***	**(1.12-1.60**	**1.55***	**(1.22-1.96)**
Japanese	2,525	**2.42***	**(1.10-5.35)**	1.28	(0.87-1.90)	0.98	(0.57-1.68)
Filipino	3,925	1.00	(0.77-1.32)	1.07	(0.92-1.25)	1.14	(0.94-1.38)

Table 3. Multivariable models predicting Gleason score among Asian men diagnosed with prostate cancer, SEER18 2004-2009

	Model 1[a]				
	Sample Size	Gleason ≥7		Gleason ≥8	
		OR[c]	95% CI	OR[c]	95% CI
All Asian	7,824	0.89	(0.79-1.01)	0.96	(0.84-1.10)
Chinese	1,538	1.15	(0.83-1.61)	1.28	(0.85-1.93)
Japanese	1,353	**1.71***	**(1.12-2.61)**	0.87	(0.55-1.36)
Filipino	2,462	0.77	(0.54-1.11)	1.03	(0.69-1.52)
	Model 2[b]				
	Sample Size	Gleason ≥7		Gleason ≥8	
		OR[c]	95% CI	OR[c]	95% CI
All Asian	14,903	1.07	(0.99-1.15)	**1.25***	**(1.13-1.37)**
Chinese	3,013	**1.26***	**(1.06-1.49)**	**1.33***	**(1.09-1.62)**
Japanese	2,525	**1.70***	**(1.14-2.53)**	1.11	(0.72-1.72)
Filipino	3,925	1.07	(0.93-1.24)	**1.26***	**(1.05-1.50)**

Table 4. Multivariable models predicting T stage among Asian men diagnosed with prostate cancer, SEER18 2004-2009

	Model 1[a]				
	Sample Size	T Stage ≥T2		T Stage ≥T3	
		OR[c]	95% CI	OR[c]	95% CI
All Asian	7,824	0.90	(0.80-1.02)	1.08	(0.90-1.30)
Chinese	1,538	1.19	(0.85-1.68)	1.36	(0.76-2.43)
Japanese	1,353	1.36	(0.90-2.05)	1.26	(0.73-2.17)
Filipino	2,462	0.82	(0.57-1.17)	0.95	(0.56-1.60)
	Model 2[b]				
	Sample Size	T Stage ≥T2		T Stage ≥T3	
		OR[c]	95% CI	OR[c]	95% CI
All Asian	14,903	0.99	(0.92-1.07)	**1.26***	**(1.12-1.41)**
Chinese	3,013	1.11	(0.94-1.32	**1.40***	**(1.07-1.83)**
Japanese	2,525	1.40	(0.94-2.07)	1.41	(0.84-2.35)
Filipino	3,925	0.92	(0.80-1.07)	0.98	(0.79-1.21)