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Trans-Pacific variation in outcomes for men treated with primary androgen-deprivation therapy (ADT) for prostate cancer

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Objectives

To compare directly survival outcomes of primary androgen-deprivation therapy (PADT) in Japan, where this treatment is endorsed by guidelines, with outcomes in the USA, where it is not.

Patients and Methods

Data were compared between men receiving PADT in the USA Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry and the Japanese Cancer of the Prostate (J-CaP) registry database. Competing risks regression was used to assess prostate cancer-specific mortality (CSM), adjusting for age, Japan Cancer of the Prostate Risk Assessment (J-CAPRA) score, diagnosis year, and treatment type [combined androgen blockade (CAB) vs castration monotherapy], comorbidity, and practice type.

Results

Men on PADT in J-CaP (13 880 men) were older than those in CaPSURE (1633 men), and had higher-risk disease (mean J-CAPRA score 3.8 vs 2.1, $P < 0.001$). They more often received CAB: 66.9% vs 46.4% ($P < 0.001$). Despite different risk profiles between the cohorts, CSM was similar on univariate analysis (log-rank $P = 0.88$). On multivariable regression, the subhazard ratio for CSM was 0.52 for J-CaP vs CaPSURE (95% confidence interval 0.40–0.68).

Conclusions

Men on PADT in Japan have less than half the adjusted CSM than those in the USA. These findings support both existing guidelines endorsing PADT in Asia and discouraging its use in the West. Elucidating the reasons behind these substantial differences, which probably include both genetic and dietary/environmental factors, may help explain the varying epidemiology of prostate cancer on either side of the Pacific.

Keywords

prostate neoplasms, androgen-deprivation therapy (ADT), risk assessment, global health, CaPSURE, J-CaP

Introduction

Primary androgen-deprivation therapy (PADT) is generally acknowledged as the preferred first-line treatment for most men with metastatic prostate cancer [1], but its use as monotherapy for clinically localised disease remains controversial. Guidelines in North America and Europe generally do not endorse PADT for non-metastatic disease except in cases of very high-risk disease [1–3], whereas Asian guidelines include PADT as an option for all men except those with very-low-risk disease [4]. Multiple studies have found that PADT use is in fact quite common around the globe, regardless of local or regional guidelines [5–10].

The Asian guideline includes several explanations for the discrepancy in its recommendation, including relatively low access both to PSA-based screening and to surgical and radiation treatment for Asian men, relatively low morbidity from PADT for Asian men, and reports of PADT efficacy in Asia that are higher than those typically observed in the USA and Europe [4]. However, no existing analyses have directly compared outcomes for PADT across these different populations. We hypothesised that PADT may in fact be more effective among Asian men in terms of cancer-specific and/or overall survival, and therefore performed a direct head-to-head comparison of risk-adjusted mortality outcomes

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for men on PADT through analysis of well-described disease registries on both sides of the Pacific: the Japanese Cancer of the Prostate (J-CaP) registry in Japan [11] and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) in the USA [12].

Patients and Methods

J-CaP accrued men diagnosed in Japan with prostate cancer (any stage) between 2001 and 2003 who were treated with ADT, either as monotherapy (PADT) or in combination with radiation or surgery. In all, 384 institutions contributed patients, comprising nearly 95% of those treated with PADT in all of Japan during this period. In all, 18.7% of the patients were treated in academic medical centres and the remainder in the community. Clinical stage was reported directly by participating urologists, who continue to report ongoing follow-up every 3 months, including information on additional treatments, progression, and both all-cause and prostate cancer-specific mortality (CSM). In all, 26 272 men were enrolled in J-CaP; of these 13 880 were treated with PADT and had complete risk stratification data available. These men were included for analysis in this study. Men receiving antiandrogen therapy alone were not included. Additional information regarding J-CaP has been published previously [11,13].

CaPSURE comprises patients accrued from 47 clinical practice sites across the USA, with 12.5% of the patients treated at academic centres. In all, 13 893 men were accrued between the cohort inception in 1995 and July 2010, of whom 1633 were treated with PADT and had complete risk stratification data available (again excluding antiandrogen monotherapy). Only 1.5% of these men were identified as of Asian descent. CaPSURE clinicians submit data on initial and subsequent PSA values, imaging results, and treatments. Additional data are acquired through regular patient surveys, and all hospitalisations trigger a medical record audit. Mortality and cause of death are determined from death certificate and National Death Index records, with adjudication of cause by central project physicians, where necessary. Additional details regarding CaPSURE have been published previously [12]. Data in both CaPSURE and J-CaP are collected and managed under local and central institutional review board supervision.

Statistical Analysis

Type of PADT was classified as orchidectomy, LHRH agonist monotherapy, or LHRH therapy together with antiandrogen [combined androgen blockade (CAB)]. In the large majority of cases, the antiandrogen component of CAB was bicalutamide 50 mg daily in CaPSURE and bicalutamide 80 mg daily in J-CaP.

The demographic and clinical characteristics were compared between J-CaP and CaPSURE using the *t*-test, chi-squared test, and Mantel–Haenszel chi-square test for trend, as appropriate. Each man's disease risk was assessed using the Japan Cancer of the Prostate Risk Assessment (J-CAPRA), a previously validated, multivariable score which assigns a 0–12 score based on PSA level (up to 3 points), biopsy Gleason score (up to 2 points), clinical T stage (up to 3 points), clinical N stage (up to 1 point), and clinical M stage (up to 3 points) . Validated score groups can be used to establish low-risk (J-CAPRA 0–2), intermediate-risk (J-CAPRA 3–7), and high-risk (J-CAPRA ≥8) groups.

The primary endpoint was CSM. Survival differences between the cohorts were initially explored through Kaplan–Meier survival curves comparing outcomes by cohort, both unstratified and stratified by J-CAPRA-score group. These unadjusted curves were compared using the log-rank statistic. Differences in CSM between J-CaP and CaPSURE were further assessed using Fine and Gray's competing risks regression. This latter analysis was controlled for risk as indicated by continuous J-CAPRA score, type of PADT (orchidectomy, LHRH monotherapy, or CAB), age at diagnosis, year of diagnosis, type of practice (academic vs community), and number of comorbidities. A subset analysis among men with high-risk disease (J-CAPRA ≥8) was also performed. To explore interactions between risk and type of PADT, additional Kaplan–Meier curves were generated for each cohort stratifying men by both PADT type and risk. All tests of statistical significance were two-tailed. Analyses were performed using Stata version 12 (Stata Corp, College Station, TX).

Results

Patient Characteristics

In all, 13 880 men in J-CaP and 1633 men in CaPSURE receiving PADT were included in the analysis. Table 1 summarises the clinical and risk characteristics of the patients receiving PADT in the J-CaP and CaPSURE registries. The patients receiving PADT in J-CaP were older than those in CaPSURE, at a mean (SD) of 75.0 (7.2) vs 72.7 (8.5) years ($P < 0.001$, *t*-test). Men in CaPSURE had a higher burden of comorbidity ($P < 0.001$, Mantel–Haenszel chi- square). Men in J-CaP were more likely to receive CAB rather than orchidectomy or LHRH agonist monotherapy ($P < 0.001$, chi-sqaured). Men in J-CaP had higher-risk disease on average than those in CaPSURE, with a median (interquartile range, IQR) PSA level of 26.9 (10.5–106.7) vs 13 (6.9–35.6) ng/mL. The mean (SD) J-CAPRA was 3.0 (3.6) in J-CaP vs 2.1 (2.3) in CaPSURE ($P < 0.001$, *t*-test). The J-CAPRA score distributions were substantially higher, as shown in Figure 1.

Mortality occurred at a mean (SD) of 70 (46) months in CaPSURE and 37 (25) months in J-CaP. The mean (SD) follow-up for censored men was 52 (40) months in CaPSURE and 45 (34) months in J-CaP. As indicated in Figure 2A,

Table 1 The patients' characteristics. All variables were statistically significantly different comparing CaPSURE to J-CaP ($P < 0.001$ by *t*-test, chi-squared, or Mantel–Haenszel chi square, as appropriate).

Variable	JCaP, *n* (%)	CaPSURE PADT, *n* (%)
Age, years:		
<55	141 (1.0)	53 (3.2)
55–65	1 211 (8.7)	252 (15.4)
66–75	5 799 (41.8)	645 (39.5)
76–85	5 811 (41.9)	604 (37.0)
>85	918 (6.6)	79 (4.8)
PSA at diagnosis, ng/mL:		
≤10	3 265 (23.5)	677 (41.5)
10.01–20	2 699 (19.5)	351 (21.5)
20.01–50	2 693 (19.4)	277 (17.0)
50.01–100	1 656 (11.9)	163 (10.0)
100.01–500	2 157 (15.5)	118 (7.2)
500.01–1000	554 (4.0)	22 (1.4)
>1000	856 (6.2)	25 (1.5)
cT stage:		
T1	2 565 (18.5)	612 (37.5)
T2	4 567 (51.4)	787 (49.2)
T3	5 302 (38.2)	190 (11.6)
T4	1 446 (10.4)	28 (1.7)
cN stage:		
Nx	818 (5.9)	1150 (70.4)
N0	10 982 (79.1)	421 (25.8)
N1	2 080 (15.0)	62 (3.8)
cM stage:		
Mx	489 (3.5)	637 (39.0)
M0	9 579 (69.0)	796 (48.7)
M1	3 812 (27.5)	200 (12.3)
Biopsy Gleason score:		
≤6	4 618 (33.3)	665 (40.7)
3 + 4	2 318 (16.7)	300 (18.4)
4 + 3	1 741 (12.5)	214 (13.1)
8	2 116 (15.2)	242 (14.8)
9–10	3 087 (22.2)	212 (13.0)
Comorbidity count, *n*:		
0	5 853 (42.2)	162 (13.7)
1	4 653 (33.5)	242 (20.5)
2	2 437 (17.6)	281 (23.8)
3	745 (5.4)	250 (21.2)
≥4	188 (1.4)	247 (20.9)
ADT type:		
Orchidectomy	749 (5.4)	105 (6.4)
LHRH agonist	3 843 (27.7)	770 (47.2)
CAB	9 288 (66.9)	758 (46.4)
Total patients	13 880 (100)	1633 (100)

univariate CSM hazards were similar between CaPSURE and J-CaP, despite the fact that men in J-CaP were substantially older and presented with higher-risk disease than those in CaPSURE. Furthermore, again despite these differences, overall mortality hazard was considerably higher in CaPSURE (Fig. 2B). The difference in overall mortality was statistically significant by log-rank ($P < 0.001$); the difference in CSM was not ($P = 0.88$).

Likewise, Figure 3A shows that CSM hazards vary as expected with increasing J-CAPRA risk group, and that at each level of risk, outcomes were substantially better in J-CaP compared with CaPSURE (all comparisons among J-CaP groups and between datasets statistically significant by log-rank, $P < 0.001$). CSM stratified by risk and PADT type are presented in Figure 3B. Minor differences in survival were noted for men with relatively low-risk disease (J-CAPRA ≤2). For those with intermediate risk (J-CAPRA 3–7) disease, men undergoing orchidectomy in J-CaP had notably worse outcomes. For those with high-risk disease (J-CAPRA ≥8), CAB was associated with better survival.

Table 2 present the results of the multivariable competing risks regression. As expected, rising J-CAPRA score was highly predictive of increased CSM, and was quite consistent between the two cohorts. Increasing age was associated with lower risk of CSM, with this association observed primarily in CaPSURE. Trends toward better survival with CAB and worse survival with orchidectomy compared with LHRH monotherapy were seen in both datasets, but these were not statistically significant. However, on a subset analysis among men with high-risk (J-CAPRA ≥8) tumours, CAB was associated with better survival than other forms of PADT [subhazard ratio (SHR) 0.71, 95% CI 0.56–0.91]. In the main analysis (Table 2), men in J-CaP faced a hazard for CSM about half of that observed in CaPSURE (SHR 0.52, 95% CI 0.40–0.68).

Discussion

In the present study of PADT mortality outcomes, we confirmed that men treated in Japan tend to be diagnosed at older ages and with higher risk and more advanced tumours than men treated in the USA. However, both cancer-specific and overall survival were substantially better for men treated in Japan compared with men treated in the USA, even after adjusting for disease risk, patient characteristics, and type of ADT. These findings reinforce the existing body of literature on PADT, which is divergent in its conclusions on either side of the Pacific.

The benefits of ADT for palliation of metastatic disease and for improving response to radiation therapy for high-risk disease are undisputed. On the other hand, in the USA and Europe, both randomised trials and nonrandomised studies have indicated clearly that for higher-risk disease, treatment protocols including local therapy yield better cancer-specific and overall survival rates than PADT alone [15,16]. In fact, even compared with conservative management, PADT improves survival only for men with high-risk disease and not for those with lower-risk disease [17]. Moreover, the potentially significant long-term impacts of such treatment have been increasingly recognised in recent years [18].

Guidelines in North America and Europe therefore do not endorse PADT for localised disease [1–3]. Nonetheless, PADT is used quite commonly, with the most frequent utilisation observed for men with higher risk tumours [19], those who would be most likely to benefit from local treatment [15]. This association between utilisation and risk appears to be at

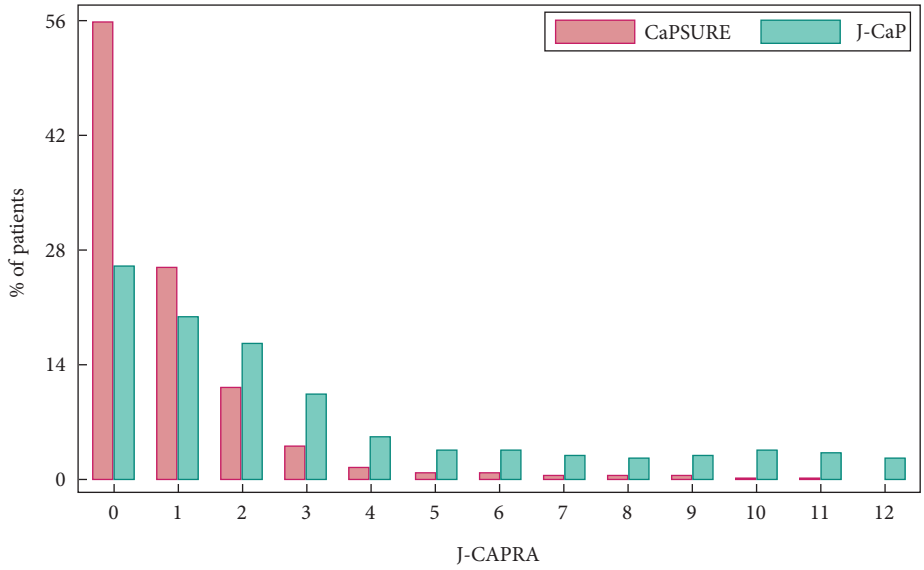


Fig. 1 Distribution of J-CAPRA scores in the CaPSURE and J-CaP registries, indicating a higher distribution of risk in J-CaP compared with CaPSURE.

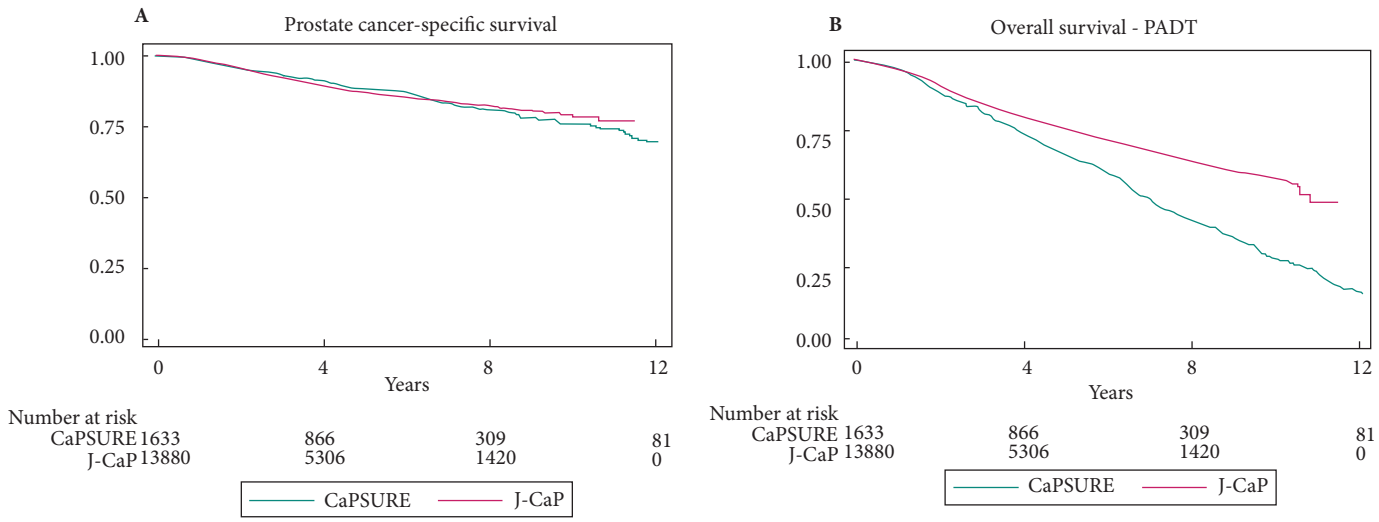
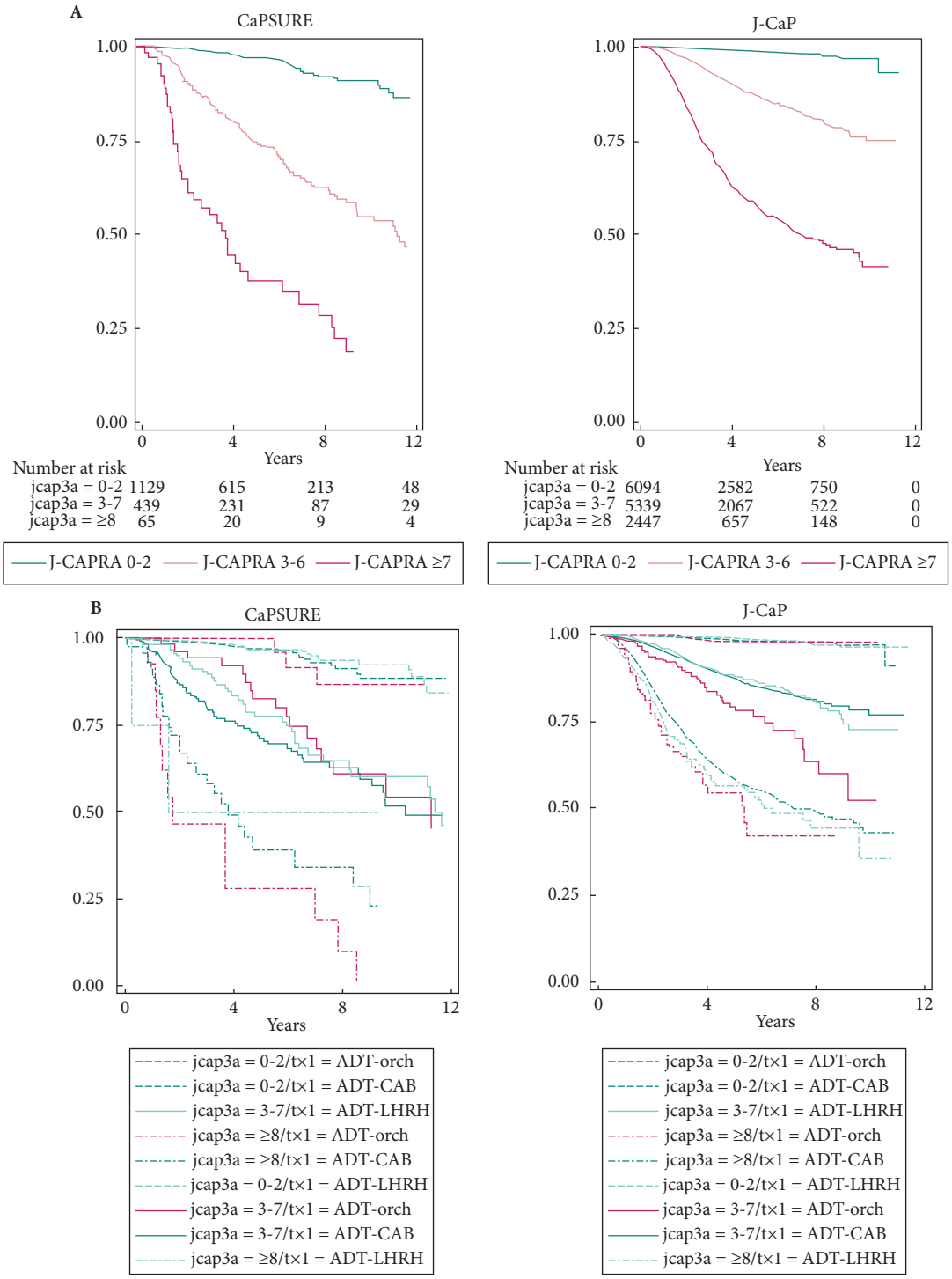


Fig. 2 Univariate Kaplan-Meier survival curves showing cancer-specific survival (**A**, $P = 0.88$, log-rank) and overall survial (**B**, $P < 0.001$, log-rank) in CaPSURE and J-CaP.

least in part driven by an age bias, as men presenting with high-risk prostate cancer tend to be older in the USA [20]. PADT is also used more commonly among men of lower socioeconomic status [19]; however, tremendous variation exists across individual clinicians in terms of their propensity to prescribe PADT, and the prescribing physician is in fact a greater source of variation than any patient or tumour factors [21]. While PADT use in the USA increased substantially throughout the 1990s [19], its use has fallen more recently, reflecting both the growing awareness of the potential side-effects of treatment, and a substantial decrease in reimbursement for ADT given in any context as of 2005 [7,9,10,22,23].

The experience with PADT in Japan, on the other hand, has been quite different. Survival differences between men receiving local therapy and those on PADT are much smaller than those seen in the USA and Europe [24,25]. PADT, furthermore, has been used more pervasively for localised disease [5,26]. Finally, ADT appears to be better tolerated in Japan, in terms of bone loss, cardiovascular risk, and other factors, than in Western populations [27–29]. Recognising these differences, the National Comprehensive Cancer Network (NCCN) Asia Consensus Statement does endorse PADT as an acceptable alternative for most men with prostate cancer, excepting those with very-low-risk disease [4].

Fig. 3 Kaplan–Meier survival curves for prostate cancer-specific survival, stratified (**A**) by J-CAPRA score group in CaPSURE (left panel, P < 0.001, log-rank) and J-CaP (right panel, P < 0.001, log-rank); and (**B**) by risk and type of PADT (orchidectomy, LHRH agonist monotherapy,or CAB) in CaPSURE (left panel) and J-CaP (right panel).



The present study results suggest that guidelines on both sides of the Pacific may be appropriate. The critical question, though, is *why* such a profound difference in response to treatment exists across these populations. The answer, while not yet clear, is almost certainly multifactorial. Differences in genetics and variation in dietary and environmental exposures

Table 2 Results of the multivariable competing risks regression for prediction of CSM.

Variable	All men		CaPSURE only		J-CaP only	
	SHR (95% CI)	*P*	SHR (95% CI)	*P*	SHR (95% CI)	*P*
Age	0.99 (0.98–1.00)	0.001	0.95 (0.93–0.97)	<0.001	0.99 (0.98–1.00)	0.05
J-CAPRA	1.39 (1.37–1.41)	<0.001	1.40 (1.32–1.49)	<0.001	1.39 (1.37–1.41)	<0.001
Year of diagnosis	0.99 (0.95–1.02)	0.46	1.01 (0.97–1.05)	0.54	0.95 (0.85–0.98)	0.009
LHRH	Ref.		Ref.		Ref.	
Orchidectomy	1.32 (1.06–1.65)	0.01	1.24 (0.74–2.09)	0.42	1.30 (1.01–1.68)	0.04
CAB	0.93 (0.82–1.08)	0.34	0.89 (0.58–1.34)	0.57	0.93 (0.80–1.07)	0.29
Academic vs community	0.99 (0.87–1.13)	0.92	1.16 (0.71–1.91)	0.59	1.05 (0.83–1.29)	0.59
Comorbidity count	0.97 (0.92–1.02)	0.29	0.99 (0.88–1.11)	0.89	1.05 (0.90–1.02)	0.19
J-CaP vs CaPSURE	0.52 (0.40–0.68)	<0.001				

almost certainly both contribute. Prostate cancer incidence among Japanese living in Hawaii is intermediate between incidence for Japanese living in Japan and Caucasians living in Hawaii. One analysis of these patterns concluded that the observed differences in incidence reflect roughly equal contributions from differences in ethnicity and geography [30].

Another study of men treated with PADT in Hawaii in the 1990s found that both overall and cancer-specific survival were significantly better for Japanese men than for Caucasian men. In that study, the benefit appeared to be greatest for those with PSA levels of <100 ng/mL at time of diagnosis [31]. For adverse effects of therapy, at least one large study has shown that in terms of adverse effects of ADT, those men with the greatest pre-treatment cardiovascular comorbidity experience the greatest risk of adverse cardiac events on ADT [32]. Better dietary habits and metabolic profiles among Japanese men, then, probably contribute to their better outcomes on ADT compared with men in the USA.

In an exploratory analysis of survival by PADT type within each risk group, we found that for men with very-high-risk disease (J-CAPRA ≥8) but not those with lower risk tumours, survival was improved for men on CAB compared with other forms of PADT. A large meta-analysis of randomised trials, primarily conducted in Western countries, comparing CAB to LHRH monotherapy, found a statistically significant but clinically modest benefit for CAB, with a HR of 0.92, corresponding to a 2.9% reduction in 5-year mortality . The most recent randomised trial of LHRH agonist monotherapy vs CAB was reported from Japan: in that trial, on multivariable analysis CAB was statistically significantly associated with improved overall mortality (HR 0.78, 95% CI 0.60–0.99) but not cancer-specific mortality (HR 0.79, 95% CI 0.55–1.11). Interestingly, in that study a univariate subset analysis suggested greater benefit for CAB compared with LHRH agonist monotherapy among men with lower stage disease [34].

Certainly, aside from database or country or origin per se, other factors, e.g. details of variations in treatment (such as different antiandrogen dose) and differences in risk, incompletely captured by the J-CAPRA may explain, at least in part, the findings we observed. Other potential sources of confounding limiting the present analysis include different methodology for comorbidity assessment (physician-reported in J-CaP, patient-reported in CaPSURE) and the fact that MRI is used much more commonly in Japan for local staging than in the USA, resulting in more common assignment of clinical stage T3 and T4 in Japan. However, these factors seem unlikely to account for the more than two-fold difference in risk-adjusted cancer-specific survival between the two cohorts.

Other important limitations to the present analysis should be acknowledged. The CaPSURE and J-CaP cohorts overlapped in terms of years of diagnosis, but CaPSURE included a wider range of years. Methods for determination of cause of death were not identical in the two cohorts. Details on duration of therapy and use of continuous vs intermittent treatment are not consistently available. A very small representation of Asian men in CaPSURE precludes a direct comparison of this group to the J-CaP cohort. Neither database includes information on continuous vs intermittent ADT, and the difference can be difficult to ascertain *post hoc*. However, the survival differences between continuous and intermittent therapy remain controversial [35], and even if utilisation patterns are different between CaPSURE and J-CaP these are unlikely to be large enough to explain observed differences in survival.

Finally, we stress that Asia is hardly monolithic in terms of genetics, environment, or prostate cancer epidemiology. Age-standardised incidence rates in Asia range from 1.4 in the Jiashan region of China to 50.2 in Israel, and from 11.3 to 22 within Japan [36]. By comparison, among Asians in the USA, the age-standardised rate is 58.0 [36], and disease presentation and risk profiles vary dramatically across various East and South Asian populations even within the state of California [37]. The NCCN Asia Consensus Statement evidence review on ADT is mostly dominated by the experience in Japan, appropriately reflecting the existing state

of the literature, and collecting data from other Asian countries will be essential looking forward. Prostate cancer is without question both a global disease and a highly heterogeneous one. Future studies should strive to encompass ever-greater geographic, ethnic, and demographic diversity.

Aside from the support we feel these findings lend to existing guidelines, these results strongly highlight the importance of recognising prostate cancer as a global disease of rising epidemiological significance [38]. Characterising and better understanding this disease's variation at the regional and global level may yield profound insights into its aetiology and biology, in order to optimise strategies for prevention, optimal screening, and treatment; and ultimately to improve outcomes for men worldwide.

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Conflicts of Interest

H.A. reports personal fees from Janssen, during the conduct of the study; and personal fees from Astellas Pharma Inc., GlaxoSmithKline K.K., Takeda Pharmaceutical Company Limited., Sanofi K.K., outside the submitted work.

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Abbreviations: (P)ADT, (primary) androgen-deprivation therapy; CAB, combined androgen blockade; CaPSURE, the Cancer of the Prostate Strategic Urologic Research Endeavor; CSM, prostate cancer-specific mortality; J-CaP, Japanese Cancer of the Prostate (registry); J-CAPRA, the Japan Cancer of the Prostate Risk Assessment; NCCN, National Comprehensive Cancer Network; SHR, subhazard ratio.

