ARTICLE

Prevalence of Prostate Cancer on Autopsy: Cross-Sectional Study on Unscreened Caucasian and Asian Men

Alexandre R. Zlotta, Shin Egawa, Dmitry Pushkar, Alexander Govorov, Takahiro Kimura, Masahito Kido, Hiroyuki Takahashi, Cynthia Kuk, Marta Kovylina, Najla Aldaoud, Neil Fleshner, Antonio Finelli, Laurence Klotz, Jenna Sykes, Gina Lockwood, Theodorus H. van der Kwast

Correspondence to: Alexandre R. Zlotta, MD, PhD, FRCSC, Department of Surgery, Division of Urology, University of Toronto, Mount Sinai Hospital and University Health Network, 60 Murray St, 6th Fl, Box 19, Toronto, Ontario, M5T 3L9, Canada (azlotta@mtsinai.on.ca).

Background   Substantial geographical differences in prostate cancer (PCa) incidence and mortality exist, being lower among Asian (ASI) men compared with Caucasian (CAU) men. We prospectively compared PCa prevalence in CAU and ASI men from specific populations with low penetrance of prostate-specific antigen screening.

Methods   Prostate glands were prospectively obtained during autopsy from men who died from causes other than PCa in Moscow, Russia (CAU), and Tokyo, Japan (ASI). Prostates were removed en-block and analyzed in toto. We compared across the 2 populations PCa prevalence, number and Gleason score (GS) of tumour foci, pathological stage, spatial location, and tumor volume using χ^2, Mann–Whitney–Wilcoxon tests, and multiple logistic regression. All statistical tests were two-sided.

Results   Three hundred twenty prostates were collected, 220 from CAU men and 100 from ASI mean. The mean age was 62.5 in CAU men and 68.5 years in ASI men ($P < .001$). PCa prevalences of 37.3% in CAU men and 35.0% in ASI men were observed ($P = .70$). Average tumor volume was 0.303cm^3. In men aged greater than 60 years, PCa was observed in more than 40% of prostates, reaching nearly 60% in men aged greater than 80 years. GS 7 or greater cancers accounted for 23.1% and 51.4% of all PCa in CAU and ASI men, respectively, ($P = .003$). When adjusted for age and prostate weight, ASI men still had a greater probability of having GS 7 or greater PCa ($P = .03$).

Conclusions   PCa is found on autopsy in a similar proportion of Russian and Japanese men. More than 50% of cancers in ASI and nearly 25% of cancers in CAU men have a GS of 7 or greater. Our results suggest that the definition of clinically insignificant PCa might be worth re-examining.

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The widespread use of prostate-specific antigen (PSA) testing has dramatically changed the prostate cancer (PCa) landscape, enhancing PCa detection at a more curable stage (1). The perverse effects of PSA testing have included the diagnosis of a considerable proportion of cancers that are probably indolent, carrying a low probability of progressing to clinically significant, lethal PCa. The lifetime risk for men in North America to be diagnosed with PCa is almost 17%, but the risk of dying from PCa is 3.4% (2).

Although men with apparent indolent disease may be offered active surveillance, data suggest overtreatment of low-risk disease is a problem, with less than 10% of men electing active surveillance in the United States (3,4). As a result, men may suffer debilitating side effects such as sexual impotence and urinary incontinence. In addition to its personal toll, overtreatment of indolent PCa also carries a substantial economic burden, which is increasing because of demographic changes (5).

Current strategies for detection and treatment of PCa will likely come under great scrutiny in the future. Increasing the body of knowledge regarding the prevalence of occult PCa and its characteristics is of utmost importance because the natural history of screen-detected PCa remains poorly understood.

Surprisingly, the contemporary prevalence of latent PCa globally is not well known (6–9). Autopsy studies have revealed a high prevalence of premalignant (high grade prostatic intraepithelial neoplasia [HGPIN]) and malignant disease (mostly low grade), starting in the third and fourth decade of life and increasing steadily thereafter (10). Autopsy studies in Asian (ASI) men are extremely limited, and contemporary data are lacking. Japanese men seem to have a prevalence of "latent" PCa similar to Caucasian (CAU) men, despite a much lower clinical incidence and mortality (11,12). Death rates from PCa in 2009 varied from the lows of less than 10 per 100 000 men in Japan to highs of more than 30 per 100 000 men in Scandinavia (13). Recent reports suggest PCa incidence in Asia, although still lower than in Western nations, is increasing rapidly, possibly because of a more Westernized lifestyle (2,14). Differences in PCa diagnostic practices are most likely the greatest contributor

to the variation in incidence rates worldwide. Comparative geographic–pathologic studies suggest that genetic, epigenetic, and environmental factors may be responsible for ethnic variations in the postinduction progression of PCa (1,11,12,15–17). Dietary factors have been incriminated to explain the discrepancy between incidental and clinically significant PCa in ASI populations (16). In many ASI countries, a change in dietary habits has occurred, and its actual impact on latent and clinical PCa deserves scrutiny.

To get further insight into the contemporary PCa prevalence on autopsy in CAU and ASI men, we compared the prevalence of PCa and HGPIN in Russian CAU and Japanese ASI men who died of causes other than PCa. We chose a specific CAU population in Russia with environmental characteristics similar to those of the Western world—reduced sun exposure and high-fat diet, both of which have been implicated in PCa risk (18,19)—but where there is no widespread PSA screening. Autopsy data in North America and Western Europe would have been heavily contaminated because of opportunistic PSA screening. Screening is also uncommon in Japan (20).

Methods

Study Population
Between 2008 and 2011, 320 prostate glands were prospectively collected during autopsy from men aged 20 to more than 80 years with no known history of PCa. The Jikei University School of Medicine, Tokyo, Japan, accrued 100 prostates from ASI Japanese men, whereas the University of Moscow, Russia, accrued 220 prostates from CAU Russian men. Ethics approval from each site was obtained before collection. Committees include Mount Sinai Hospital Research Ethics Board (08-0029-E), University Health Network Research Ethics Board (08-0092-CE), Ethics Committee of the Jikei University School of Medicine for Biomedical Research [19–157(5088)], and the Ethics Committee of the Moscow State University of Medicine and Dentistry. Patient demographics (age, race, date of death, and cause of death) were recorded. Consent was obtained from relatives in all cases.

Prostate Handling
Analogous methodology was followed in Tokyo and Moscow. Prostate glands were removed en-block with the seminal vesicles within 24 hours of death, immediately injected with buffered formalin (pH 7.3), and placed in solution for 2 days at room temperature. Patients who died more than 24 hours before prostate harvesting were excluded. Prostate glands were weighed and sectioned at 4-mm intervals perpendicular to the posterior surface and placed in buffered formalin for an additional 24 hours. The slices were cut in four quadrants to allow for standardized embedding in routine cassettes for further processing and for PCa and multifocality mapping. Tissue sections were embedded in paraffin, and conventional sections were stained with hematoxylin and eosin.

Pathological Assessment
PCa identification, Gleason score (GS), and presence of HGPIN and intraductal carcinoma were assessed by one experienced uropathologist (T. van der Kwast) in a blinded fashion, according to

morphologic criteria described previously (21,22). The number of tumor foci and spatial location (peripheral, transition, anterior zone) were recorded according to the criteria of McNeal et al. (23,24) using appropriate sectioning planes. An area of carcinoma was considered to be a separate focus if it was separated from the nearest adjacent focus by a low-power field diameter (4.5 mm) (25). All cancers were reviewed twice and confirmed for grade and pathological extent.

Volumetric assessment
Each tumor focus was outlined on the slides, and its surface measured using a standard Aperio image analyzer. Volume estimation for each tumor focus was calculated by measurement of tumor area in each section using virtual microscopy. Cancer volumes were calculated by multiplying the tumor area by the section thickness (4mm). Total tumor volume was calculated as the sum of the volumes of the individual foci.

Statistical Analysis
The prevalence of PCa and HGPIN was compared between ASI and CAU men using χ^2 tests. GS trend was analyzed with the Cochran–Armitage test, whereas age, average number of PCa foci, average PCa volume, and average weight were analyzed as continuous variables and compared using Student t tests or Mann–Whitney–Wilcoxon tests. Multiple logistic regression was used to estimate the probability of having PCa, adjusting for possible confounders such as age, race, and prostate weight. All statistical tests were two-sided, and a P value less than .05 was used to assess statistical significance. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Power Calculation
Based on estimates of PCa prevalence on autopsy from the literature (7,8,12), we estimated the sample to include 200 CAU prostates and 100 ASI prostates. With these sample sizes, an α of 0.05, a power of 80%, and assuming a prevalence of 30% for the CAU population (17), a difference of 15% can be detected between groups using a test to compare proportions with a continuity correction. A sample size of 200 CAU men allowed the 95% confidence interval (CI) of the PCa prevalence to be estimated with a precision of ±7% and a precision of ±10% for the ASI group (n_2 = 100).

Results

Characteristics of the subjects are shown in Table 1. Three hundred twenty prostates were collected, 220 from CAU men and 100 from ASI men. ASI men were older than CAU men (mean age = 62.5 and 68.5 years in CAU and ASI men, respectively; $P < .001$), and ASI prostates weighed less than CAU prostates ($P = .001$). Despite a similar methodology, the weight per block of harvested and processed prostate was statistically significantly different between ASI and CAU prostates ($P < .001$, Wilcoxon test). Median weight per block was 2.23 g (standard deviation [SD] = 0.42) and 3.54 g (SD = 1.59) in ASI and CAU prostates, respectively ($P = .001$).

A total of 117 (35.6%) cancers were identified (Table 1), with no statistically significant difference between ASI and CAU men ($P = 0.70$). The median age of the ASI and CAU population with

Table 1. Baseline characteristics of patients*

Characteristics	Mean (range) or No. (%)			
	ASI n = 100	CAU n = 220	Total cohort n = 320	P
Age, years	68.5 (24–89)	62.5 (22–80)	64.4 (22–89)	<.001†
History of cancer, non-PCa	59 (59.0)	26 (11.8)	85 (26.5)	<.001
Prostate weight, g	31.9 (10.2–144.5)	40.0 (13.2–150.6)	37.5 (10.2–150.6)	.001†
Prostate cancer	35 (35)	82 (37.3)	117 (35.6)	.70
Gleason score				.02‡
4	0 (0.0)	4 (4.9)	4 (3.4)	
5	1 (2.9)	10 (12.2)	11 (9.4)	
6	16 (45.7)	49 (59.8)	65 (55.6)	
7	14 (40.0)	16 (19.5)	30 (25.6)	
8	2 (5.7)	3 (3.7)	5 (4.3)	
9	2 (5.7)	0 (0.0)	2 (1.7)	
7–10	18 (51.4)	19 (23.2)	37 (31.6)	.003‖
8–9	4 (11.4)	3 (3.6)	7 (6.0)	.05
Focality§				
Unifocal	24 (68.6)	59 (72.0)	83 (70.9)	.66
Multifocal	9 (25.7)	18 (22.0)	27 (23.1)	
Tumor volume				
Tumor volume, cm³	0.423 (0.009–2.575)	0.252 (0.0052–2.52)	0.303 (0.0052–2.575)	.2†
Tumor volume <0.5 cm³	27 (77.1)	67 (81.7)	94 (80.3)	.57
Tumor volume > 0.5 cm³	8 (22.9)	15 (18.3)	23 (19.7)	
Clinically insignificant	17 (48.6)	58 (70.7)	75 (64.1)	.02
Clinically significant	18 (51.4)	24 (29.3)	42 (35.9)	
Tumor location‡				
Peripheral zone	16 (45.7)	42 (51.2)	58 (49.6)	.59
Transitional zone	9 (25.9)	17 (20.7)	26 (22.2)	.55
Peripheral + transitional zone	7 (20.0)	13 (15.9)	20 (17.1)	.59
Other/unknown	3 (8.6)	10 (12.2)	13 (11.1)	
Anterior zone	7 (20.0)	18 (21.9)	25 (21.4)	.81
Intraductal	4 (11.4)	3 (3.7)	7 (5.98)	.19
pT3 or extraprostatic extension	4 (11.5)	9 (10.98)	13 (11.1)	.94
Perineural invasion	4 (11.5)	5 (6.1)	9 (7.7)	.45
HGPIN	39 (39.0)	70 (31.8)	109 (34.1)	.21

* ASI=Japanese Asian; CAU = Russian Caucasian; PCa = Prostate Cancer; HGPIN = High Grade Prostatic Intraepithelial Neoplasia. All tests were two-sided.

† Mann–Whitney–Wilcoxon test to determine if there is a difference in medians between the two cohorts.

‡ Cochran–Armitage test- examining whether distribution over Gleason score of cancers differs between the two cohorts.

§ For some tumors, we were unable to identify focality/tumor location.

‖ Analysis of percentage of Gleason score of 7 to 10 vs percentage of Gleason score 4 to 6.

PCa was 74.8 and 65.5 years, respectively (P < .001). After controlling for differences in age and prostate weight, the cohorts did not differ in their probability of PCa (P = .30). This was not statistically significantly related to prostate size when adjusted for differences in age and cohort (P = 0.24).

PCa prevalences of 37.3% and 35.0% were observed in CAU and ASI men, respectively (P = 0.70). PCa prevalence increased with age in both ASI and CAU men (Figure 1). The youngest ASI and CAU men with PCa were aged 53 and 33 years, respectively. Older men were more likely to have PCa (odds ratio [OR] =1.04; 95% CI = 1.02 to 1.06; P < .001). In a multivariable model testing for an interaction between age and race, a borderline statistically significant P value was observed (P = .07), suggesting that the odds of having PCa in older patients was lower in CAU men than in ASI men.

Eighty-three (70.9%) of the cancers were unifocal, and 27 (23.1%) were multifocal (Table 1). There was no statistically significant difference in the number of foci or location between ASI and CAU men (all P > .05). Interestingly, 25 (21.4%) men had a focus in the anterior zone.

Overall, 31.6% of cancers had a GS of 7 or greater, with a statistically significantly higher proportion of GS 7 or greater PCa in ASI men (51.4%) than in CAU men (23.1%; P = .003). After controlling for differences in age and prostate weight, ASI men still had a statistically significantly higher probability of having GS 7 or greater PCa (P = .03).

Table 2 presents a breakdown of pathological results according to each decade of life. In men aged more than 60 years, PCa was observed in more than 40% of prostates, reaching nearly 60% in men aged more than 80 years. GS 7 or greater disease started later in life in ASI men compared with CAU men. The percentage of GS 7 or greater PCa increased with age. Nine of 16 (56.2%) PCa in ASI men aged 71 to 80 years had GS 7 or greater disease. In the same age group, 10 of 34 (29.4%) CAU tumors were GS 7 or greater (P = .07), whereas 70% of tumors from ASI men aged 81 to 90 years were GS 7 or greater. There were no CAU men aged 81 to 90 years in the study.

Table 3 presents the prevalence of GS 7 or greater cancers in ASI and CAU men aged 50 to 80 years. In the group aged 50 to 70 years, eight (8%) CAU and two (5%) ASI men had GS 7 or greater PCa, steeply increasing to nine (25%) and 10 (13%) of
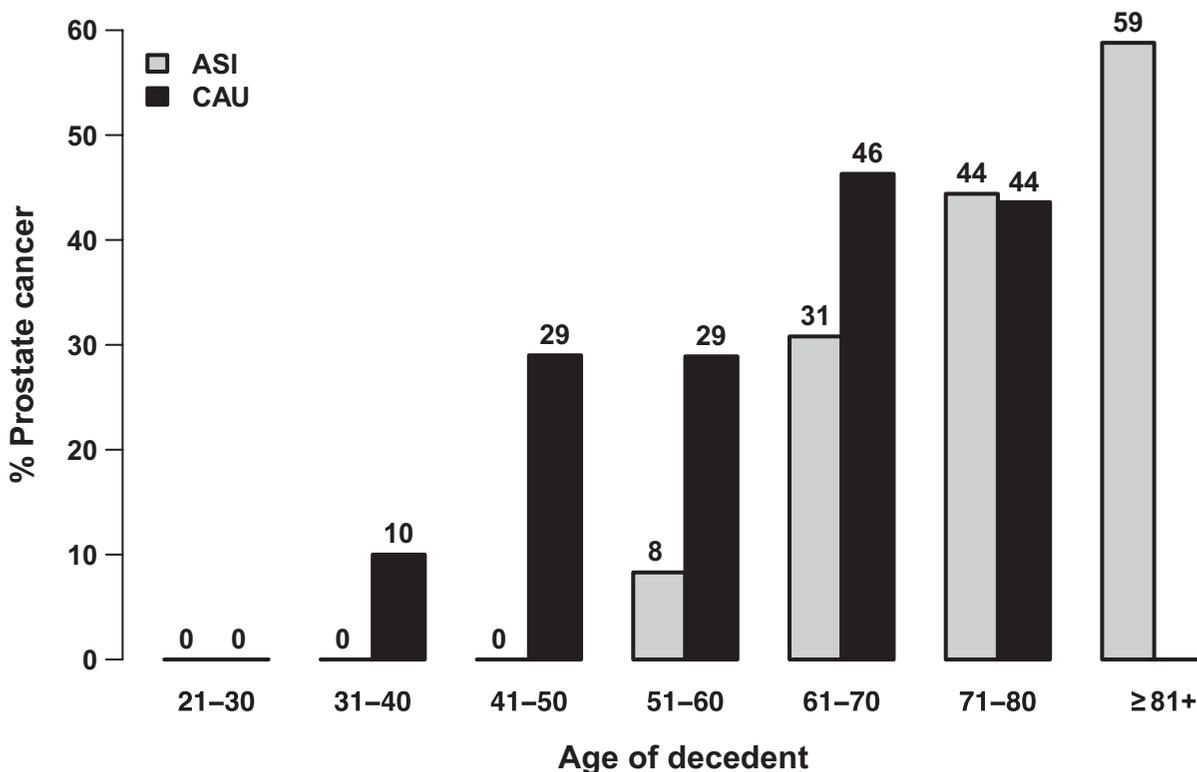
Figure 1. Prostate cancer prevalence distribution by age range. ASI =Japanese Asian men; CAU = Russian Caucasian men.

the ASI and CAU men in the group aged 70 to 80 years. Breaking down GS 7 into (3+4) or (4+3), among 14 GS 7 in ASI, 13 were 3+4 and one was 4+3. Among 16 CAU with GS 7, 10 and six were 3+4 and 4+3, respectively, (P = .09).

Tumor volumes ranged from 0.0052 to 2.58 cm^3 (Table 1). Average tumor volume was 0.303 cm^3. All eight large tumors (>0.5 cm^3) were GS 7 or greater among ASI men. No ASI man had a GS 6 tumor larger than 0.149 cm^3. Among CAU men, out of 15 tumors larger than 0.5 cm^3, five (33.3%) were GS 6 or less. There were more clinically significant tumors according to the Epstein criteria among ASI men (18; 51.4%) than among CAU men (24; 29.3%; P = .02) but not when adjusting for age (OR = 2.02; P = .12).

Thirteen (11.1%) men presented with extra-prostatic extension, (P = .94) (Table 1). Fifty-nine (59.0%) ASI men had a history of other cancers compared with 26 (11.8%) CAU men (P < .001) (Table 1). This difference was seen both in prostates with PCa (62.9% vs 12.2%) and those without PCa (56.9% vs 11.6%).

There was no statistically significant difference between ASI and CAU men with respect to HGPIN (P = .21) (Table 1), but the difference between the percentage of prostates without PCa that had HGPIN (24.5%) and the percentage of prostates with PCa that had HGPIN (50.4%; P < 0.001) was statistically significant. This difference was seen in both cohorts and was statistically significant in each.

Discussion

In contrast with many other solid tumors, the discrepancy between the prevalence of latent disease, clinically diagnosed tumors, and mortality due to PCa suggests that a large proportion of tumors are not destined to become life-threatening (26,27). Both European and US randomized trials on PCa screening have outlined the risks of overdiagnosis and overtreatment of latent cancers (4,28,29).

Our cross-sectional study was carried out on contemporaneously and consecutively collected autopsy specimens from 2 continents, employing a standardized methodology for harvesting prostate glands and centralized pathologic grading and staging. Cohorts were selected from populations with a low penetration of PSA screening. This lowered the risk of artifactual reduction in the number of PCa due to antemortem screen-detected PCa (30). We chose a specific population of CAU men in Moscow with environmental/dietary characteristics likely similar to neighboring Scandinavia, which has one of the highest rates of PCa mortality (31). Alcohol intake is particularly high in Russia, and cirrhosis is common, which may induce hyperestrogenism and testicular atrophy. Although this could influence PCa risk, studies have not supported the hypothesis of a decreased PCa risk in men with alcoholic cirrhosis (32).

In our study, the overall PCa prevalence was 37% in CAU men, which is similar to other reports (6,7). Haas et al. (33) observed a PCa prevalence of 29% in 164 men, 92% of whom were CAU men (Table 4). The mean age of the patients in Haas's cohort (64 years) does not explain their lower prevalence. However, this US study was performed after PSA screening became prevalent. Several European studies showed a lower prevalence than our study (8,9) (Table 4). Study design, demographic differences, and thickness of the step sections during prostate processing may explain some

Table 2. Breakdown of pathological results per each decade of life*

Age, years	Cohort			Prostate cancer			PIN		
	ASI, No.	CAU, No.	Total, No.	ASI, No. (%)	CAU, No. (%)	Total, No. (%)	ASI, No. (%)	CAU, No. (%)	Total, No. (%)
21–30	1	2	3	0	0	0	0	0	0
31–40	5	10	15	0	1 (10.0)	1 (6.7)	0 (0.0)	1 (10.0)	1 (6.7)
41–50	3	31	34	0	9 (29.0)	9 (26.5)	1 (33.3)	6 (19.4)	7 (20.6)
51–60	12	45	57	1 (8.3)	13 (28.9)	14 (24.6)	2 (16.7)	14 (31.1)	16 (28.1)
61–70	26	54	80	8 (30.8)	25 (46.3)	33 (41.2)	11 (42.3)	18 (33.3)	29 (36.3)
71–80	36	78	114	16 (44.4)	34 (43.6)	50 (43.9)	17 (47.2)	31 (39.7)	48 (42.1)
81–90	17	0	17	10 (58.8)	0 (0.0)	10 (58.8)	8 (47.1)	0 (0.0)	8 (47.1)
Total	100	220	320	35 (35)	82 (34.6)	117 (36.6)	39 (39)	70 (31.9)	109 (34.1)

Age, years	Cohort			Total GS ≥7			Mean tumor volume, mm³		
	ASI, No.	CAU, No.	Total, No.	ASI, No. (%)	CAU, No. (%)	Total, No. (%)	ASI, mean (range)	CAU, mean (range)	Total, mean (range)
21–30	0	0	0	—	—	—	—	—	—
31–40	0	1	1	—	0	0	—	9.6	9.6
41–50	0	9	9	—	1 (11.1)	1 (11.1)	—	30.4 (6.0–531.6)	30.4 (6.0–531.6)
51–60	1	13	14	0	4 (30.8)	4 (28.6)	19.2	220 (10.0–1017.9)	131.2 (10.0–1017.9)
61–70	8	25	33	2 (25.0)	4 (16.0)	6 (18.2)	46.9 (9.0–858.0)	73.6 (5.6–2243.2)	54.0 (5.6–2243.2)
71–80	16	34	50	9 (56.2)	10 (29.4)	19 (38.0)	156.4 (9.2–1405.2)	70.8 (5.2–2520.0)	76.4 (5.2–2520.0)
81–90	10	0	10	7 (70.0)	—	7 (70.0)	280.9 (31.2–2575.2)	—	280.9 (31.2–2575.2)
Total	35	82	117	18 (51.4)	19 (23.2)	37 (31.6)	130.4 (9–2572.2)	61.6 (5.2–2520.0)	69.6 (5.2–2575.2)

* ASI = Japanese Asian; CAU = Russian Caucasian; GS = Gleason score; PIN = prostatic intraepithelial neoplasia; —data not available.

Table 3. Prevalence of Gleason score 7 or greater cancers in Asian and Caucasian men (core group aged 50–80 years)

Age, years	Asian men		Caucasian men		
	HG*, No.	% HG	HG*, No.	% HG	P
51–60	0/1	0	4/13	30.8	.99
61–70	2/8	25	4/25	16.0	.62
51–70	2/9	22.2	8/38	21.1	.99
71–80	9/16	56.3	10/34	29.4	.12

* HG = high grade/ Gleason score of 7 or greater.

of these discrepancies (6–9) because thinner sections increase the detection of small tumors.

PCa prevalence in CAU men appears to have remained stable over the last decades. In 1954, 31% of American men aged more than 50 years who died from other causes had evidence of PCa (34). Very little research on latent PCa has been conducted among ASI populations.

In our study, the prevalence of PCa on autopsy in ASI men was similar to that in CAU men, but the age distribution was different. Our observations support the concept that at the latent microscopic stage, ASI and CAU men have a similar PCa prevalence. These findings suggest that the initial step in the induction of PCa in Japanese men is similar to that in CAU men. In Japanese men from Hawaii (35), PCa was identified on autopsy in 27% of men who died after age 50 years, reaching a frequency of 63% among men aged more than 80 years. In our study, figures were comparable: 23.7% and 58.8%, respectively. In previous reports on Japanese men aged 50 years or older, the autopsy prevalence was reported as only 8.7% (36).

The striking and novel observation in our ASI population was that a staggering 51.4% of autopsy PCa tumors were GS 7 or greater, most of them GS 7 (3+4). Among those aged more than 70 years, a high proportion of ASI and CAU men (44%) were found to have PCa. Although ASI men had a higher percentage of GS 7 or greater disease, they developed it later in life than CAU men. There were no CAU men aged more than 80 years in our study, whereas 17% of the ASI men were in that age range. One explanation is the difference in life expectancy. In 2010, the average life expectancy for Russian males was 63.0 years (37), whereas in Japan, it was 79.6 years (38). GS 8 and 9 tumors were rare but not exceptional in our autopsy study (n = 7 of 320; prevalence = 2.2%).

In one recent US autopsy study, 30% of cancers were GS 7 or greater (33), higher than the proportion observed in our CAU cohort (23%). Other autopsy studies (7–9), performed before the 2005 International Society of Urological Pathology (ISUP) Gleason modification was introduced, found rates between 3.7% and 12.5% (40) (Table 4). Among 248 CAU men undergoing radical cystoprostatectomy for muscle-invasive bladder cancer and no history or clinical evidence of PCa before surgery, 13% had GS 7 or greater PCa (40).

In the two large, randomized trials on PCa screening (age range = 55–75 years), the proportion of diagnosed GS 7 or greater cancers was 30% (3). It has been suggested that PCa shows a grade increase over time, and this might account for the observed high prevalence of GS 7 or greater PCa among ASI men aged more than 70 years (41). A GS 7 PCa in a 75-year-old man might not carry

the same prognosis as in a younger patient. Also, the high number of GS 7 or greater PCa observed in our study may have been the result of Gleason scoring modification, leading to an upgrading to GS 7 of some previously diagnosed GS 6 tumors (39). The natural clinical evolution of GS 7 tumors is not uniform. PCa mortality represents a relatively modest contributor to all-cause mortality among men diagnosed with localized low- and intermediate-risk PCa (41–43).

One of the criticisms of PCa screening is that it results in a more frequent detection of small-volume, low-grade, and organ-confined PCa, often called indolent or clinically insignificant (17,44). Many of these tumors have the histological characteristic of the autopsy tumors we observed among CAU men. However, most of the autopsy tumors were unifocal, which seems to contrast with tumor multifocality observed in screening studies. Wolters et al. compared screen-detected tumors with PCa identified in cystoprostatectomy specimens. Screen-detected T1c PCa were more often multifocal (73% vs 37%) and less frequently clinically insignificant (33% vs 81%) (45). The morphological characteristics of PCa in our study matched those reported by Sanchez-Chapado and by Sakr (6,8)—namely, differentiated small tumors preferentially located in the peripheral zone of the prostate in younger age groups that became bulkier or more diffuse with age. Unifocality could possibly be a characteristic of latent/clinically insignificant PCa, but this remains a hypothesis at this stage.

Our results also suggest that the definition of clinically insignificant PCa could be re-examined, as its requirements are possibly too stringent. More than half of PCa found in our study in Japan and 30% of tumors in CAU were intermediate grade or nonorgan confined and thus clinically significant according to current criteria.

Our study has several limitations. The number of ASI men included is relatively limited, and we had few young men. Our results are drawn from autopsies performed in men who died at the hospital of other causes, many from other cancers in our ASI cohort. This may not represent the general population. Whether these cancers resulted in a high rate of premature death that could have blunted the clinical significance of GS 7 or greater disease in this group is unknown. The age of our ASI and CAU cohorts was different, with ASI men being older on average. Also, despite an overall similar prevalence of PCa among ASI and CAU men and the same methodology to harvest the prostates, there was a difference in the prostate weight per block, and therefore we may have slightly underestimated the prevalence of PCa in CAU men.

It is puzzling that although ASI men have a similar prevalence of latent PCa to CAU men and a higher proportion of latent GS 7 PCa found on autopsy, they have a lower mortality from the disease, although it should be kept in mind that most were detected at an older age. The challenge is to understand the factors implicated in the progression to metastatic disease. Recently, both the incidence and mortality rates of PCa in ASI countries have been increasing, suggesting changes in the natural history of the disease. In Japan, this trend is expected to continue because the younger generations, who are eating a more Westernized diet, are aging. Consequently, previous low death rates might also be changing in the future.

Table 4. Comparison of clinico-pathological characteristics among other published studies*

	Haas et al. (33)	Sanchez-Chapado et al. (8)	Satmatiou et al. (9)	Soos et al. (7)	This study, ASI	This study, CAU	This study, all
Cohort	164, United States	146, Spain	212, Greece, impalpable PCa	142, Hungary	100, Japan	220, Russia	320
Age, years, mean (range)	64 (54–73)‡	48.5 (20–80)	—	—	68.5 (24–89)	62.5 (22–80)	64.4 (22–89)
Prostate cancer, No. (%)	47 (29)	27 (18.5)	40(18.8)	54 (38.8)	35 (35)	82 (37)	117 (35)
PIN, No. (%)		42 (28.7)	57 (26.9)	44 (31.6)	39 (39)	70 (32)	109 (34)
GS ≤ 6, No. (%)	32 (70)	26 (96)	35 (87.5)	58 (92)	17 (49)	63 (77)	80 (68)
GS ≥ 7, No. (%)	14 (30)	1 (3.7)	5 (12.5)	6 (8)	18 (51)	19 (23)	37 (32)
Tumor volume, cm³, mean (range)	0.13 (0.04–0.37)‡	—	—	—	0.423 (0.009–2.575)	0.252 (0.0052–2.52)	0.303 (0.0052–2.575)
Clinically insignificant, No. (%)	27 (57)	—	—	—	17 (48.6)	57 (69.5)	75 (64.1)
Clinically significant, No. (%)	20 (43)	—	—	19 (35.2)†	18 (51.4)	25 (30.5)	42 (35.9)
Unifocal, No. (%)	51%	17 (48.5)	16 (40)	44 (82.5)	24 (68.6)	59 (72.0)	83 (70.9)
Multifocal, No. (%)	49%	—	24 (60)	10 (18.5)	9 (25.7)	18 (22.0)	27 (23.1)
pT3, No. (%)	6 (13)	2 (74)	4 (10.0)	—	4 (11.5)	9 (10.98)	13 (11.1)
Ant Zone, No. (%)	31 (36)	—	—	—	7 (20)	18 (21.9)	25 (21.37)
Pz, No. (%)	54 (62)	19 (70.4)	35 (87.5)	82.8 foci	16 (45.7)	42 (51.2)	58 (49.6)
Tz, No. (%)	14 (16)	2 (74)	1 (2.5)	18.2 foci	9 (25.9)	17 (20.7)	26 (22.2)
Pz + Tz, No. (%)	2 (2)	4 (14.8)	4 (10)	—	7 (20.0)	13 (15.9)	20 (17.1)

* Ant zone = anterior zone; ASI = Japanese Asian; CAU = Russian Caucasian; GS = Gleason score; IQR = interquartile range; PIN = prostatic intraepithelial neoplasia; Pz = peripheral zone; Tz = transitional zone; —data not available.

† Tumor volume > 0.5 cm³.

‡ Value reported as median (IQR).

Our findings also have implications for study design and analyses involving genetic markers for PCa risk or diagnostic markers. Any control group is likely to be contaminated by a substantial percentage of latent PCa, even GS 7 or greater.

Our results support that efforts should be directed toward a better biological characterization of PCa and reinforce concerns about overdiagnosis and overtreatment. The ubiquity of microscopic PCa, both low and intermediate grade, contrasts too sharply with the low risk of fatal disease.

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Notes

Affiliations of authors: Department of Surgery, Division of Urology, Mount Sinai Hospital, Toronto, ON, Canada (ARZ, CK); Department of Surgical Oncology, Urology (ARZ, CK, NF, AF, GL) and Department of Radiation Oncology (JS), Princess Margaret Hospital, University Health Network, Toronto, ON, Canada; Department of Urology, Jikei University School of Medicine, Tokyo, Japan (SE, TK, MK, HT); Department of Urology, University of Moscow, Moscow, Russia (AG, MK); Department of Pathology, Toronto General Hospital, University Health Network, Toronto, ON, Canada (NA, TvdK); Division of Urology, Sunnybrook and Women's Health Science Centre, Toronto, ON, Canada (LK).