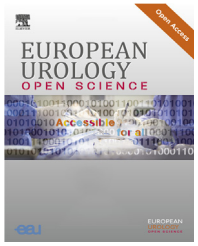
available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Prostate Cancer

Comparison of Characteristics, Follow-up and Outcomes of Active Surveillance for Prostate Cancer According to Ethnicity in the GAP3 Global Consortium Database

Kerri Beckmann[a,b,*], *Aida Santaolalla*[a,c], *Jozien Helleman*[d], *Peter Carroll*[e], *Byung Ha Chung*[f], *Lui Shiong Lee*[g], *Antoinette Perry*[h], *Jose Rubio-Briones*[i], *Mikio Sugimoto*[j], *Bruce Trock*[k], *Riccardo Valdagni*[l,m], *Prokar Dasgupta*[c,n], *Mieke Van Hemelrijck*[a,c], *Oussama Elhage*[c,n], *the Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance GAP3 Consortium*[1]

[a] *Translational Oncology and Urology Research, King's College London, London, UK;* [b] *Cancer Epidemiology and Population Health University of South Australia, Adelaide, Australia;* [c] *Guy's and St Thomas' NHS Foundation Trust, London, UK;* [d] *Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [e] *Department of Urology, UCSF – Helen Diller Comprehensive Cancer Center, University of California, San Francisco, CA, USA;* [f] *Department of Urology, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Korea;* [g] *Department of Urology, Sengkang General Hospital and Singapore General Hospital, Singapore;* [h] *University College Dublin, Dublin, Ireland;* [i] *Instituto Valenciano de Oncología, Valencia, Spain;* [j] *Faculty of Medicine, Kagawa University, Kagawa, Japan;* [k] *Johns Hopkins University, The James Buchanan Brady Urological Institute, Baltimore, MD, USA;* [l] *Department of Oncology and Hemato-oncology, Università degli Studi di Milano, Milan, Italy;* [m] *Radiation Oncology and Prostate Cancer Program, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [n] *Immunology and Microbial Sciences, King's College London, London, UK*

Article info

Article history:
Accepted September 28, 2021

Associate Editor:
Guillaume Ploussard

Keywords:
Prostate cancer
Active surveillance
Race
Ethnicity
Outcomes

Abstract

Background: Studies of active surveillance (AS) for prostate cancer (PCa) have focussed predominantly on Caucasian populations. Little is known about the experience of Asian men, while suitability for men of African descent has been questioned.
Objective: To compare baseline characteristics, follow-up, and outcomes for men on AS for PCa, according to ethnicity.
Design, setting, and participants: The study cohort included 13 centres from the GAP3 consortium that record ethnicity (categorised broadly as Caucasian/white, African/Afro-Caribbean/black, Asian, mixed/other, and unknown). Men with biopsy grade group >2, prostate-specific antigen (PSA) >20 ng/ml, T stage ≥cT3, or age >80 yr were excluded.
Outcome measurements and statistical analysis: Clinical characteristics, follow-up schedules, outcome status, and reasons for discontinuation were compared across ethnic groups. Risk of upgrading, potential disease progression (grade group ≥3 or T stage ≥3), suspicious indications (any upgrading, number of positive cores >3, T stage ≥cT3, PSA >20 ng/ml, or PSA density >0.2 ng/ml/cc^2), and conversion to treatment were assessed using mixed-effect regression models.

[1] The Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) consortium members are presented in the Supplementary material.

* Corresponding author at: Level 8 SAHMRI Building, North Terrace, Adelaide, South Australia 5001, Australia. Tel.: +61 8 83027018.
E-mail addresses: kerri.beckmann@unisa.edu.au, kerri.beckmann@kcl.ac.uk (K. Beckmann).

https://doi.org/10.1016/j.euros.2021.09.012

Results and limitations: The eligible cohort (n = 9158) comprised 83% Caucasian men, 6% men of African descent, 5% Asian men, 2% men of mixed/other ethnicity, and 4% men of unknown ethnicity. Risks of suspicious indicators (hazard ratio = 1.27; 95% confidence interval [CI] 1.12–1.45), upgrading (odds ratio [OR] = 1.40; 95% CI 1.14–1.71), and potential progression (OR = 1.46; 95% CI 1.06–2.01) were higher among African/black than among Caucasian/white men. Risk of transitioning to treatment did not differ by ethnicity. More Asian than Caucasian men converted without progression (42% vs 26%, p < 0.001). Heterogeneity in surveillance protocols and racial makeup limit interpretation.
Conclusions: This multinational study found differences in the risk of disease progression and transitioning to treatment without signs of progression between ethnic groups. Further research is required to determine whether differences are due to biology, sociocultural factors, and/or clinical practice.
Patient summary: This international study compared prostate cancer active surveillance outcomes by ethnicity. Risks of upgrading and disease progression were higher among African than among Caucasian men. Transitioning to treatment without progression was highest among Asian men. Understanding of these differences requires further investigation.

1. Introduction

In the USA, African-American men are 1.6 times more likely to develop prostate cancer (PCa) and twice as likely to die from the disease as the general population [1]. Similar incidence and mortality patterns are seen elsewhere, particularly among West African descendants, including in the UK and the Caribbean [2,3]. Men of African descent may also develop more aggressive disease [4–6] and be at a greater risk of disease progression after curative treatment [7]. Possible explanations for their poorer outcomes include differences in genetics or tumour biology, delayed diagnosis, increased comorbidity, lack of access to treatment, and poorer quality of care [8].

In the UK, incidence of PCa among men of African descent is five times that among Caucasian men [9]. Conversely, British Asians have a lower PCa incidence and are more likely to have clinical features reflecting early-stage disease [10]. While men of African descent appeared to receive more intensive investigation and are more likely to undergo radical treatment, variation in treatment patterns in the UK was minimal after adjusting for age [11].

While outcomes for non-Caucasian men undergoing active surveillance (AS) are of considerable interest, few studies have examined differences according to ethnicity. Several small single-institute [12,13] or local area-based studies from the USA [14] have reported higher rates of progression and transition to treatment among African-American men than among Caucasian men. Data from Korea suggest that a considerable proportion of Asian men who would be eligible for AS according to western-based criteria may harbour more aggressive disease [15].

The aim of this study was to describe the baseline characteristics, follow-up received, and outcomes for men with very low, low, and favourable intermediate-risk PCa on AS, according to broad ethnicity groupings (ie, Caucasian, Asian, and African origin) using data from the Global Action Plan Prostate Cancer Active Surveillance (GAP3) database, the largest collection of AS data worldwide. Outcomes assessed include the risk of conversion to treatment, indication of potential disease progression, and grade reclassification.

2. Patients and methods

2.1. Study participants

This study used data from the Movember Foundation's GAP3 database (v3.2, November 2019), a world-wide, centralised database on AS for PCa [16]. Currently, GAP3 has records for over 20 000 men from 28 collaborating centres across Europe, UK, USA, Canada, Asia, and Australia, who were followed prospectively. Each contributing institution was responsible for obtaining ethical approvals for sharing of deidentified patient-level data in the GAP3 database.

While data items in GAP3 have been standardised, criteria for inclusion, follow-up schedules, and protocols for transitioning to treatment vary across centres. Most follow-up schedules include serial prostate-specific antigen (PSA) monitoring, digital rectal examination (DRE), and repeat biopsies, at different frequencies, to monitor disease progression. Magnetic resonance imaging (MRI) is also part of routine follow-up in some centres. Data collected in GAP3 include baseline demographics and tumour characteristics (eg, age, race/ethnicity, biopsy grade group, clinical stage, PSA, number of biopsy cores taken/positive for PCa, prostatic volume, and PSA density), follow-up measures (eg, PSA/PSA kinetics, biopsy findings, T stage at DRE, and findings on MRI), status at last follow-up (continuing AS, converted to active treatment, switched to watchful waiting, lost to follow-up, or died), reasons for stopping AS, and subsequent treatments.

Our study included all men in the GAP3 database (enrolled during 1995–2018) from 11 centres that recorded race/ethnicity, plus those in the Seoul and Kagawa cohorts (all confirmed as Asian men). Men with baseline characteristics inconsistent with most AS inclusion criteria were excluded (ie, grade >3 + 4, PSA >20 ng/ml, stage ≥cT3, and age >80 yr at diagnosis). Details of participating centres are provided in Supplementary Table 1.

Categories for race/ethnicity in GAP3 include Caucasian/white, African American/black, Asian, mixed race, Pacific Islander, native American, other, and refused. Contributing centres classified individual patients' ethnicity according to their own criteria. For analysis, mixed race (n = 25), Pacific Islander (n = 2), native American (n = 7), and other (n = 187) ethnicities were collapsed into a single "mixed/other" category,

with "refused" and missing data classified as "unknown", resulting in five broad ethnic groupings: Caucasian/white, African descent/black, Asian, mixed/other, and unknown.

Study outcomes included the following: risk of conversion to active treatment, measured as the time from enrolment to discontinuation of AS to undergo curative or palliative treatment, including radical prostatectomy, radiotherapy, or hormone therapy; risk of upgrading from biopsy grade group at any repeat biopsy; risk of disease progression (grade group ≥3 or T stage ≥cT3); and time to first suspicious indicator, defined as any upgrading from biopsy grade, more than three positive cores (or >33% positive cores), clinical T3 on DRE, PSA >20 ng/ml, or PSA density >0.2 ng/ml/cc during follow-up, regardless of whether men transitioned to treatment or not. PSA density calculations were based on prostate volume at diagnosis, without adjustment for increasing volume over time, due to insufficient follow-up data on PSA density or prostate volume. Radiological changes were not included as outcome measures since too few centres report MRI findings during follow-up.

2.2. Analysis

Descriptive analyses were undertaken comparing clinical characteristics, AS status at 3 and 5 yr, reasons for discontinuing AS, conversion to active treatment without disease progression, and transitioning to active treatment without evidence of upgrading, across ethnic groups. Time on AS and frequency of monitoring (PSA testing and biopsy procedures) were described using Kaplan-Meier methods.

To determine whether the risk of converting to active treatment or the risk of developing an indication of potential disease progression differed by ethnicity, we undertook mixed-effects survival regression models, applying Weibull distribution and assigning random intercepts for treatment centre. Censoring occurred at the time of death, switch to watchful waiting (ie, no active monitoring with noncurative treatment if symptoms arise), loss to follow-up, or the last follow-up date if still on AS. Models were adjusted for age (5-yr age groups), diagnostic period (1995–2004, 2005–2009, 2010–2014, and 2015–2018), diagnostic method (transrectal ultrasound guided biopsies, transperineal guided biopsies [TPs], and transurethral resection of the prostate [TURP]), and clinical characteristics at diagnosis—grade group (2 vs 1), clinical stage (T2 vs T1), PSA concentration (<5, 5–9.9, 10–14.9, and 15–20 ng/ml), prostate volume (continuous per 10 ng/cc [3]), number of cores sampled (continuous), and number of positive cores (continuous). We assessed the risk of upgrading at any follow-up biopsy and the risk of potential disease progression among men who had undergone one or more repeat biopsies, using mixed-effects logistic regression, with random intercepts for treatment centre (level 2). These models included adjustment for time from enrolment to repeat biopsy (months, continuous) plus the above listed covariates.

Missing data for covariates were imputed using multiply imputed chain equations (for details, see Supplementary Table 2). All analyses were conducted using Stata v15 (Stata Corp, TX, USA).

3. Results

Participant selection is shown in Supplementary Fig. 1. Of the 9158 eligible men, 7569 (83%) were classified as Caucasian, 592 (6%) as of African descent, 448 (5%) as Asian, 221 (2%) as mixed/other, and 328 (4%) as of unknown

Table 1 – Characteristics of the eligible study cohort, by ethnicity

Characteristics at diagnosis	Caucasian	African descent	Asian	Mixed/other	Unknown
Total, *n* (%)	7569 (83)	592 (6)	448 (5)	221 (2)	328 (4)
Age (yr)					
Median (IQR)	65 (60–69)	63 (56–69)	66 (61–71)	64 (57–68)	64 (58–69)
No. (% missing)	5 (0)	3 (0)	0 (0)	0 (0)	3 (1)
PSA (ng/ml)					
Median (IQR)	5.2 (4.0–7.0)	5.4 (4.0–7.3)	5.5 (4.2–8.0)	5.1 (4.0–6.7)	5.4 (4.1–7.4)
No. (% missing)	209 (3)	21 (4)	7 (2)	6 (3)	15 (5)
Grade group, no. (%)					
1	6939 (92)	520 (88)	404 (90)	205 (93)	287 (88)
2	630 (8)	72 (12)	44 (10)	16 (7)	41 (12)
No. (% missing)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
T stage, no. (%)					
cT1	5128 (83)	365 (85)	343 (90)	123 (79)	227 (81)
cT2	1015 (17)	63 (15)	42 (10)	33 (21)	53 (19)
No. (% missing)	1426 (19)	164 (28)	106 (24)	65 (29)	5 (1)
Diagnostic method, no. (%)					
TRUS biopsy	5982 (79)	485 (82)	296 (67)	114 (52)	198 (60)
Transperineal biopsy	1352 (18)	85 (15)	75 (17)	105 (47)	123 (38)
TURP	235 (3)	21 (4)	75 (17)	2 (1)	7 (2)
No. of cores taken					
Median (IQR)	12 (12–14)	12 (12–13)	12 (11–15)	12 (12–16)	12 (12–14)
No. (% missing)	1027 (14)	68 (11)	106 (24)	30 (14)	18 (5)
Positive cores					
Median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
No. (% missing)	418 (6)	32 (5)	103 (24)	4 (18)	17 (5)
Prostate volume					
Median (IQR)	43 (32–60)	44 (33–66)	35 (28–48)	40 (30–57)	42 (29–62)
No. (% missing)	1519 (20)	224 (37)	127 (28)	30 (14)	106 (32)
Diagnosis period, no. (%)					
1995–2004	835 (11)	49 (8)	21 (5)	30 (14)	14 (4)
2005–2009	1793 (24)	104 (18)	87 (19)	64 (29)	44 (14)
2010–2014	2719 (36)	221 (37)	272 (61)	91 (41)	135 (41)
2015–2018	2222 (29)	218 (37)	68 (15)	36 (16)	135 (41)
No. (% missing)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)

IQR = interquartile range; PSA = prostate-specific antigen; TRUS = transrectal ultrasound guided biopsies; TURP = transurethral resection of the prostate.
Details for imputed values are provided in Supplementary Table 2.

Table 2 – Status at 3 and 5 yrs after commencing AS, by ethnicity

	Caucasian(n = 7569) No. (%)	African descent (n = 592) No. (%)	Asian (n = 448) No. (%)	Mixed/other(n = 221) No. (%)	Unknown(n = 328) No. (%)
Status at 3 yr [a]					
Still on AS	3362 (44)	212 (36)	196 (44)	113 (51)	117 (36)
Censored <3 yr (still on AS)	2178 (29)	227 (38)	133 (30)	53 (24)	168 (51)
Converted to WW	21 (0.3)	2 (0.3)	0 (0)	0 (0)	2 (0.6)
Died	27 (0.4)	3 (0.5)	3 (0.7)	1 (0.5)	1 (0.4)
Lost to follow-up	48 (0.6)	6 (1)	1 (0.2)	3 (1)	0 (0)
Converted to treatment	1993 (26)	142 (24)	115 (26)	51 (23)	40 (12)
Status at 5 yr[a]					
Still on AS	1949 (26)	102 (17)	84 (19)	71 (32)	57 (17)
Censored <5 yr (still on AS)	3039 (40)	304 (51)	219 (49)	82 (37)	213 (65)
Converted to WW	42 (0.6)	2 (0.3)	1 (0.6)	0 (0)	2 (0.6)
Died	58 (0.7)	4 (0.7)	4 (0.7)	2 (0.9)	1 (0.3)
Lost to follow-up	93 (1)	7 (1)	3 (0.6)	4 (2)	0 (0)
Converted to treatment	2396 (32)	173 (29)	137 (31)	62 (28)	55 (17)

AS = active surveillance; WW = watchful waiting (no longer on formal surveillance with intention to curatively treat disease progression due to advanced age or comorbidities).
[a] Log-rank test for difference by ethnicity <0.001.

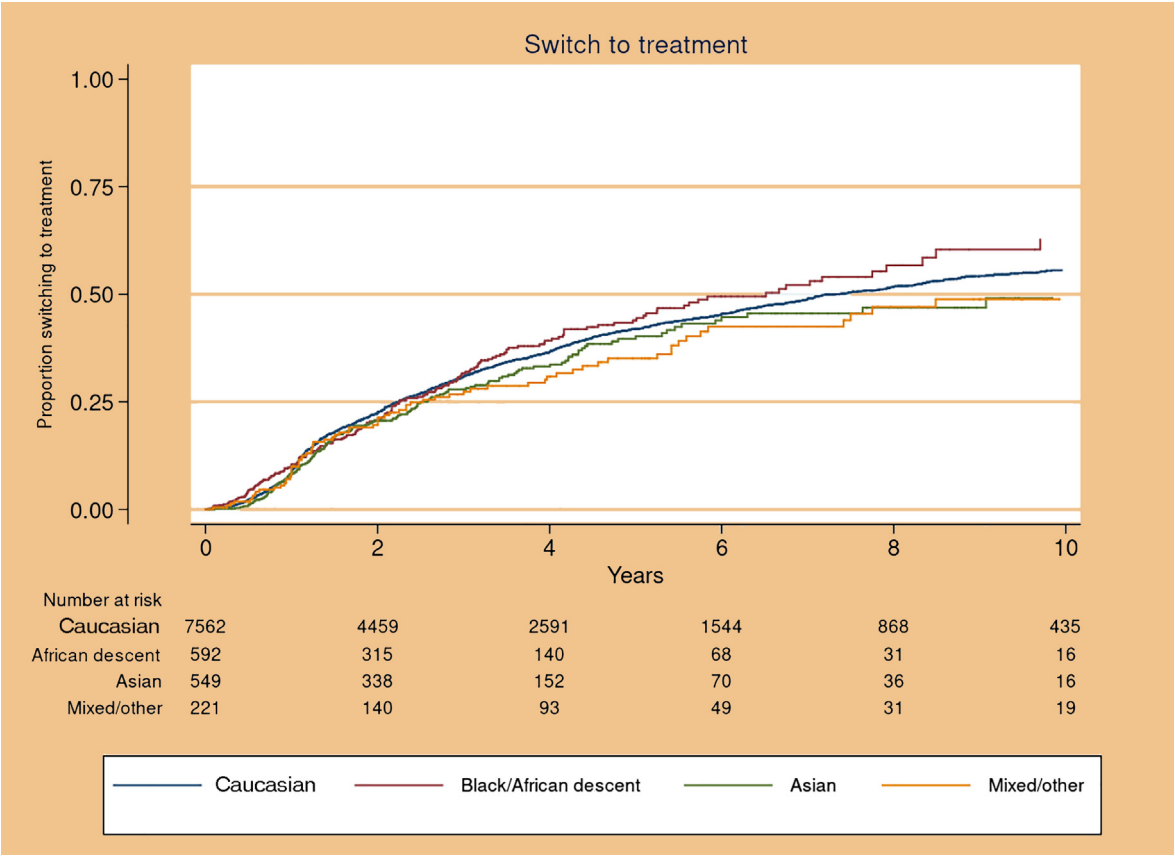


Fig. 1 – Conversion to treatment among men on active surveillance for prostate cancer, according to ethnicity.

ethnicity. Men of African descent were predominantly from centres in the USA (76%), while Asian men were predominantly from centres in Asian countries (71%).

As shown in Table 1, clinical characteristics at diagnosis were generally similar across ethnicity groups. However, a higher proportion of Asian men were diagnosed via TURP (17% among Asian men compared with 3% among Caucasians and 4% among men of African descent). A higher proportion of men of African descent than Caucasian and Asian men were diagnosed during the most recent period (2015–2018).

Men's status at 3 and 5 yr after commencing AS was similar across the different ethnicities (with the exception of the unknown category), as shown in Table 2. The only major difference across groups pertained to the proportions censored while still on AS. Including censored cases, the proportions of men still on AS at 3 yr were 73%, 74%, 74%, and 75%, and pro-

portions converting to active treatment were 26%, 24%, 26%, and 23%, for Caucasian, African descent, Asian, and mixed/other ethnicities, respectively. Similar consistency was seen at 5 yr. The relative consistency in proportions converting to treatment over time was also evident in the cumulative incidence curve presented in Fig. 1.

Detailed data on events and outcomes during follow-up while on AS are presented in Table 3. The median follow-up time for Caucasian men (who comprised the majority of the study cohort) was 2.6 yr. During this period, 75% of Caucasian men had undergone one or more biopsies (mean number 2.3; standard deviation 1.7). Of these men, 32% experienced upgrading from original biopsy grade at any subsequent biopsy, while 16% were upgraded at their first repeat biopsy. Of all Caucasian men, 46% developed some suspicious indicator (eg, any upgrading, more than three positive cores [or >33%], PSA density >0.2, PSA >20 ng/ml, and clinical T stage ≥T3, collectively) that could signal disease progression during the course of follow-up. Of the 36% men who converted to active treatment, 26% had converted to treatment without any suspicion of progression or without disease progression being reported as the reason for converting. Of the Caucasian men, 14% did not convert to active treatment following upgrading/grade reclassification.

Compared with Caucasian men, men of African descent had shorter follow-up (median 2.2 yr) and fewer had undergone a biopsy (64%; mean number 1.9) during follow-up. Of those biopsied, a slightly greater proportion were upgraded at their first repeat biopsy (20% vs 16%, $p = 0.005$). However, there was no difference between the proportion of men of African descent and that of Caucasian/white men who developed any indicators of potential disease progression (48% vs 46%) or converted to active treatment (33% vs 36%). Among men with evidence of disease progression, a marginally higher proportion of men of African descent did not transition to treatment, though this was not statistically significant (36% vs 30%, $p = 0.237$).

Fewer Asian men underwent any follow-up biopsy (53%; mean number 1.7). Among those biopsied, a higher proportion were upgraded at their first repeat biopsy (22% compared with 16% among Caucasian men, $p = 0.237$). Overall, fewer Asian men developed potential indications of progression than men of other ethnicities (38% compared with 46% among Caucasian men, $p = 0.001$). While the proportions converting to active treatment were similar between groups (Asian 33%, Caucasian 36%, and African descent 33%), a larger proportion of Asian men who converted did so without signs of disease progression (42% vs 26% among Caucasian men, $p < 0.001$).

Results of the multivariable mixed-effect survival regression models, adjusted for differences in baseline characteristics and clustering by centre, showed no statistically significant difference in the risk of converting to treatment by ethnicity (Table 4 and full models in Supplementary Table 3). However, differences were observed for the risk of developing suspicious indicators, with men of African descent having a higher risk than Caucasian men (hazard ratio 1.27; 95% confidence interval [CI] 1.12–1.45). In the logistic regression model assessing the risk of upgrading, all other ethnic groups were more likely to experience upgrading than Caucasian men. However, the increase was statistically significant only for men of African descent (odds ratio [OR] 1.40; 95% CI 1.14–1.71). Models for potential disease progression (ie, grade group ≥3 or T stage ≥3 during follow-up) also indicated an increased risk among men of African descent (OR 1.46; 95% CI 1.06–2.01) compared with Caucasian men.

4. Discussion

Findings from our analyses of GAP3 data, the largest collection of international AS data, indicate no difference in the risk of transitioning to treatment according to ethnicity, after accounting for baseline differences. However, the

Table 3 – Follow-up events among men on active surveillance for prostate cancer, by ethnicity

	Caucasian (n = 7569)	African descent (n = 592)	Asian (n = 448)	Mixed/other (n = 221)	Unknown (n = 328)
Follow-up events					
Follow-up time (yr; all eligible men)), median (IQR)	2.6 (1.2–3.7)	2.2 (1.1–3.9)	2.5 (1.3–4.3)	3.1 (1.2–5.6)	2.3 (1.0–3.9)
Men with ≥1 follow-up biopsy, n (% among all eligible men)	5665 (75)	381 (64)	238 (53)	187 (85)	209 (64)
Number of biopsies (men with ≥1 follow-up biopsy), mean (SD)	2.3 (1.6)	1.9 (1.4)	1.7 (1.2)	2.6 (1.7)	2.1 (1.3)
Number of PSA tests (all eligible men), median (IQR)	7 (4–14)	5 (3–9)	6 (4–11)	7 (4–14)	5 (3–11)
Suspicious indicators					
Any upgrade at any follow-up biopsy (% of men with ≥1 follow-up biopsy)	1799 (32)	136 (36)	86 (36)	70 (37)	76 (36)
Upgrade/reclassification at 1st repeat biopsy (% of men with ≥1 follow-up biopsy)	881 (16)	78 (20)	53 (22)	27 (14)	32 (15)
Increase to ≥4 positive cores (% of men with ≥1 follow-up biopsy)	1672 (29)	134 (35)	75 (32)	80 (43)	79 (38)
Increase to >33% positive cores (% of men with ≥1 follow-up biopsy)	1224 (22)	87 (23)	44 (19)	62 (33)	54 (26)
Grade group ≥3 at any follow-up biopsy (% of men with ≥1 follow-up biopsy)	535 (9)	44 (12)	26 (11)	25 (14)	21 (10)
Increase to PSA density >0.2 ng/ml/cc (% of all eligible men)	1663 (22)	135 (23)	85 (19)	58 (26)	69 (21)
T stage ≥cT3 (% of all eligible men)	10 (0.3)	1 (0.2)	0 (0)	0 (0)	0 (0)
Any suspicious indicators[a] (% of all eligible men)	3514 (46)	287 (48)	173 (38)	132 (59)	146 (44)
Outcomes					
Converted to active treatment (% of eligible men)	2751 (36)	194 (33)	148 (33)	73 (33)	64 (20)
Upgraded but did not convert to treatment (% of men who upgraded)	535 (30)	47 (36)	28 (33)	36 (51)	51 (67)
Converted to treatment without report or suspicion of disease progression (% of men who converted to treatment)	707 (26)	60 (31)	63 (43)	8 (11)	20 (31)

IQR = interquartile range; PSA = prostate-specific antigen; SD = standard deviation.

[a] Any suspicious indictors defined as presence of any of the following indications during follow-up: any upgrading, four or more positive cores, >33% positive cores, PSA >20 ng/ml, PSA density >0.2, and cT3 at clinical examination. PSA density was based on imputed values for prostate volume for 22% of the study cohort. Individuals may have multiple indicators.

Table 4 – Risk of conversion to active treatment, developing suspicious indicators, and upgrading at any follow-up biopsy

Ethnic group	Conversion to treatment[a] (9151 men)		Any suspicious indication[a] (9151 men)		Upgrading at any follow-up biopsy[b] (14 985 biopsies/6680 men)		Potential disease progression[b] (14 985 biopsies/6680 men)	
	HR	95% CI	HR	95% CI	OR	95% CI	OR	95% CI
Caucasian	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
African descent	1.08	0.93–1.26	1.27	1.12–1.45	1.40	1.14–1.71	1.46	1.06–2.01
Asian	0.93	0.71–1.22	0.96	0.78–1.19	1.12	0.83–1.51	1.23	0.81–1.87
Mixed/other	0.82	0.64–1.04	1.08	0.90–1.28	1.23	0.96–1.57	1.40	0.96–2.04
Unknown	0.71	0.55–0.91	0.96	0.81–1.14	1.08	0.86–1.37	1.19	0.80–1.75

CI = confidence interval; DRE = digital rectal examination; HR = hazard ratio; PSA = prostate-specific antigen.
Suspicious indication: defined as any upgrade from biopsy grade, number of positive core >3 or >33%, PSA >20 ng/ml, PSA density >0.2, and stage ≥cT3 on DRE, that is, first of any of these events.
Upgrading: defined as upward reclassification of diagnostic grade group at any repeat biopsy.
Potential disease progression: defined as grade group ≥3 or stage ≥cT3.
[a] Mixed-effect survival regression (Weibull distribution/random intercept) adjusted for age, diagnostic grade, clinical stage, number of cores taken, number of cores positive, prostate volume, and year of diagnosis, grouped by centre (imputed data).
[b] Mixed-effect logistic regression adjusted for age, grade, clinical stage, number of cores taken, number of cores positive, prostate volume, year of diagnosis, and months to follow-up biopsy, grouped by centre and person (imputed data).

likelihood of upward grade reclassification and potential disease progression during follow-up appeared to be higher among African/Afro-Caribbean/black men than among Caucasian/white men. The proportion transitioning to treatment, despite no evidence of upgrading or suspicion of progression, was highest among Asian men.

Cautious interpretation of these findings is warranted. GAP3 data are drawn from multiple centres in different regions of the world, which have very heterogeneous policies and practices with respect to inclusion criteria, follow-up, and recommendations for switching to treatment. While several other studies have presented findings suggesting that African-American men with low-risk disease have greater risks of disease progression and transitioning to treatment when on AS [12,17,18], questions have been raised about whether factors such as inferior diagnostic workup has led to erroneous conclusions [19]. For example, using data from the SEARCH database, which comprises data from six Veterans Affairs medical centres offering "equal access" care, Leapman et al [20] found no evidence of increased risk of upgrading (serious upgrading) or upstaging among African-American men compared with Caucasian men with clinically low-risk PCa who underwent radical prostatectomy. Similarly, a recent study, the Prostate Cancer Active Surveillance Study (PASS), in which standardised protocols were applied, the risk of grade reclassification was similar for African-American and Caucasian-American men [21]. Furthermore, Riviere et al [22] found no difference in 10-yr PCa mortality between African-American men and non-Hispanic white men who received guideline compliant care via the Veterans Affair health care system.

Although we lacked data on some diagnostic procedures (eg, MRI and/or confirmatory biopsy before enrolment), our results suggest slightly less intense workup among men of African descent, with fewer of these men receiving a TP diagnostic biopsy than men of other ethnicities. Furthermore, baseline characteristics indicated slightly more men of African descent with Gleason 3 + 4, which is associated with a greater risk of progression [23]. Even if differences in grade reclassification among men of African descent are due to differences in the type or quality of diagnostic workup, increased risks of upgrading and progression among men of African descent on AS indicates the need for careful monitoring, ideally with repeat biopsy during the early phases of AS, to confirm suitability for AS [24].

While the risk of transitioning to treatment was similar across ethnic groups, a higher proportion of Asian men converted in the absence of signs of progression or upgrading. This may reflect regional or centre-based differences in follow-up protocols or triggers for treatment, which are not adequately captured in GAP3 data. For example, some centres (including one Asian-based centre) have MRI-based follow-up protocols with differing criteria for conversion to treatment. Alternatively, cultural differences in acceptable levels of risk among Asian clinicians or patients, or a negative impact on quality of life as reported in an Asian AS cohort [25], may have led to higher dropout rates. Concerns that Asian men who are classified as low risk using "Western criteria" may harbour more aggressive disease, which are supported by evidence from the Korea PCa registry [15], may contribute to higher withdrawal from AS.

Our findings contradict expectations of higher levels of conversion due to more stringent criteria being applied to men of African descent, given evidence suggesting they may have more aggressive disease [4,5,26]. The possibility that some men of African descent prefer to remain on AS despite signs of progression, in order to avoid side effects (eg, sexual dysfunction), should not be dismissed [27]. Alternatively, if a greater proportion of men of African descent sought active treatment outside of urology clinics (eg, undergo radiotherapy rather than prostatectomy, as has been reported [28]), risk of transitioning to treatment may be underestimated due to some cases being recorded as "lost to follow-up".

Heterogeneity in protocols for AS inclusion, surveillance, and treatment triggers, as well as differences in reporting reasons for progression across participating cohorts, is a major limitation of this study. While we have accounted for clustering by centre in multivariable models, differences in rates of biopsy and PSA follow-up may have impacted our findings. Moreover, heterogeneity within ethnicity cate-

gories [29] may have influenced our findings, most likely biasing results towards the null. For example, Asian men include those from centres in Asian countries (Singapore, Korea, and Japan), British Asians (predominantly from South Asia), and Asian Americans (who form a diverse ethnic group). Insufficient numbers prevented separate regional analyses. In addition, median follow-up time in GAP3 was relatively short, limiting long-term assessment of outcomes. Furthermore, the length of follow-up and the proportion not having undergone further biopsy differ between groups. Our inability to investigate the influence of MRI due to a lack of data may limit the generalisability of findings in an era where imaging is frequently used in diagnostic workup and follow-up. We were unable to disentangle the effects of socioeconomic disparities since very few participating centres reported measures of deprivation. The authors also acknowledge the complexity of such research, that race is a poor biological construct, and concerns about race as a study variable [29,30].

5. Conclusions

This large international study found no difference in the risk of transitioning to treatment among men on AS for PCa according to ethnicity. While we observed increased risks of upgrading and disease progression among men of African descent, these results should be interpreted with caution given likely differences in diagnostic workup and social disadvantage. However, our findings indicate the need for careful monitoring of men of African descent who undergo AS. A large, well-conducted prospective study, in which all men receive best practice diagnostic workup and are monitored according to standardised protocols, is required to adequately assess the differences in AS outcomes according to ethnicity. The greater tendency to transition to treatment without evidence of disease progression among Asian men should also be investigated further to reduce overtreatment in this group.

***Author contributions*:** Kerri Beckmann had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Elhage, Dasgupta, Van Hemelrijck, Beckmann.

Acquisition of data: None.

Analysis and interpretation of data: Beckmann, Santaolalla, Helleman, Carroll, Chung, Lee, Perry, Rubio-Briones, Sugimoto, Trock, Valdagni, Dasgupta, Van Hemelrijck, Elhage.

Drafting of the manuscript: None.

Critical revision of the manuscript for important intellectual content: Beckmann, Santaolalla, Helleman, Carroll, Chung, Lee, Perry, Rubio-Briones, Sugimoto, Trock, Valdagni, Dasgupta, Van Hemelrijck, Elhage.

Statistical analysis: Beckmann, Santaolalla.

Obtaining funding: None.

Administrative, technical, or material support: Helleman.

Supervision: None.

Other: None.

Financial disclosures: Kerri Beckmann certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** This work was supported by the Movember Foundation. The funder did not play any role in the study design, collection, analysis or interpretation of data, or drafting of this paper. Dr. Kerri Beckmann is supported by a National Health and Medical Research Council (Australia) Sydney Sax Fellowship (Gnt#1124210).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2021.09.012.

References

[1] Altekruse SF, Huang L, Cucinelli JE, McNeel TS, Wells KM, Oliver MN. Spatial patterns of localized-stage prostate cancer incidence among white and black men in the southeastern United States, 1999–2001. Cancer Epidemiol Biomarkers Prev 2010;19:1460–7.

[2] Odedina FT, Akinremi TO, Chinegwundoh F, et al. Prostate cancer disparities in black men of African descent: a comparative literature review of prostate cancer burden among black men in the United States, Caribbean, United Kingdom, and West Africa. Infect Agent Cancer 2009;4(Suppl 1):S2.

[3] Persaud S, Goetz L, Beurnett A. Active surveillance for prostate cancer: Is it ready for primetime in the Caribbean. Afr J Urol 2017;23:89–93.

[4] Tsodikov A, Gulati R, de Carvalho TM, et al. Is prostate cancer different in black men? Answers from 3 natural history models. Cancer 2017;123:2312–9.

[5] Powell IJ, Bock CH, Ruterbusch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. J Urol 2010;183:1792–6.

[6] Kim HS, Moreira DM, Jayachandran J, et al. Prostate biopsies from black men express higher levels of aggressive disease biomarkers than prostate biopsies from white men. Prostate Cancer Prostatic Dis 2011;14:262–5.

[7] Evans S, Metcalfe C, Ibrahim F, Persad R, Ben-Shlomo Y. Investigating black-white differences in prostate cancer prognosis: a systematic review and meta-analysis. Int J Cancer 2008;123: 430–5.

[8] McGinley KF, Tay KJ, Moul JW. Prostate cancer in men of African origin. Nat Rev Urol 2016;13:99–107.

[9] Metcalfe C, Evans S, Ibrahim F, et al. Pathways to diagnosis for black men and white men found to have prostate cancer: the PROCESS cohort study. Br J Cancer 2008;99:1040–5.

[10] Metcalfe C, Patel B, Evans S, et al. The risk of prostate cancer amongst South Asian men in southern England: the PROCESS cohort study. BJU Int 2008;102:1407–12.

[11] Evans S, Metcalfe C, Patel B, et al. Clinical presentation and initial management of black men and white men with prostate cancer in the United Kingdom: the PROCESS cohort study. Br J Cancer 2010;102:249–54.

[12] Abern MR, Bassett MR, Tsivian M, et al. Race is associated with discontinuation of active surveillance of low-risk prostate cancer: results from the Duke Prostate Center. Prostate Cancer Prostatic Dis 2013;16:85–90.

[13] Kelly SP, Van Den Eeden SK, Hoffman RM, et al. Sociodemographic and clinical predictors of switching to active treatment among a large, ethnically diverse cohort of men with low risk prostate cancer on observational management. J Urol 2016;196:734–40.

[14] Odom BD, Mir MC, Hughes S, et al. Active surveillance for low-risk prostate cancer in African American men: a multi-institutional experience. Urology 2014;83:364–8.

[15] Jeong CW, Hong SK, Byun SS, et al. Selection criteria for active surveillance of patients with prostate cancer in Korea: a multicenter analysis of pathology after radical prostatectomy. Cancer Res Treat 2018;50:265–74.

[16] Bruinsma SM, Zhang L, Roobol MJ, et al. The Movember Foundation's GAP3 cohort: a profile of the largest global prostate cancer active surveillance database to date. BJU Int 2018;121:737–44.
[17] Cohn JA, Dangle PP, Wang CE, et al. The prognostic significance of perineural invasion and race in men considering active surveillance. BJU Int 2014;114:75–80.
[18] Iremashvili V, Soloway MS, Rosenberg DL, Manoharan M. Clinical and demographic characteristics associated with prostate cancer progression in patients on active surveillance. J Urol 2012;187:1594–9.
[19] Ehdaie B, Carlsson S, Vickers A. Racial disparities in low-risk prostate cancer. JAMA 2019;321:1726–7.
[20] Leapman MS, Freedland SJ, Aronson WJ, et al. Pathological and biochemical outcomes among African-American and Caucasian men with low risk prostate cancer in the SEARCH database: implications for active surveillance candidacy. J Urol 2016;2016(196):1408–14.
[21] Schenk JM, Newcomb LF, Zheng Y, et al. African American race is not associated with risk of reclassification during active surveillance: results from the Canary Prostate Cancer Active Surveillance Study. J Urol 2020;203:727–33.
[22] Riviere P, Luterstein E, Kumar A, et al. Survival of African American and non-Hispanic white men with prostate cancer in an equal-access health care system. Cancer 2020;126:1683–90.
[23] Musunuru HB, Yamamoto T, Klotz L, et al. Active surveillance for intermediate risk prostate cancer: survival outcomes in the Sunnybrook experience. J Urol 2016;196:1651–8.
[24] Bosco C, Cozzi G, Kinsella J, et al. Confirmatory biopsy for the assessment of prostate cancer in men considering active surveillance: reference centre experience. Ecancermedicalscience 2016;10:633.
[25] Hirama H, Sugimoto M, Miyatake N, et al. Health-related quality of life in Japanese low-risk prostate cancer patients choosing active surveillance: 3-year follow-up from PRIAS-JAPAN. World J Urol 2021;39:2491–7.
[26] Ha YS, Salmasi A, Karellas M, et al. Increased incidence of pathologically nonorgan confined prostate cancer in African-American men eligible for active surveillance. Urology 2013;81:831–5.
[27] Machirori M, Patch C, Metcalfe C, Kay N. Study of the relationship between Black men, culture and prostate cancer beliefs. Cogent Med 2018;5:1442636.
[28] Moses KA, Paciorek AT, Penson DF, Carroll PR, Master VA. Impact of ethnicity on primary treatment choice and mortality in men with prostate cancer: data from CaPSURE. J Clin Oncol 2010;28:1069–74.
[29] Ioannidis JPA, Powe NR, Yancy C. Recalibrating the use of race in medical research. JAMA 2012;325:623–4.
[30] Boyd R, Lindo E, Weeks L, et al. On racism: a new standard for publishing on racial inequalities. Health Affairs Blog 2020.