Racial disparities in the care of patients with advanced prostate cancer: an analysis of patient-reported outcome and experience measures

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"Racial Disparities in the Care of Patients with Advanced Prostate Cancer: An Analysis of Patient-Reported Outcome and Experience Measures"

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Racial disparities in the care of patients with advanced prostate cancer: an analysis of patient-reported outcome and experience measures

A dissertation presented by

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Abstract

In the US, an estimated 120,000 individuals are living with advanced prostate cancer, defined as metastatic hormone sensitive prostate cancer (mHSPC) or castration resistant prostate cancer (CRPC). Black individuals experience the most significant advanced prostate cancer burden with over double the age-adjusted prevalence and mortality compared to White individuals. Previous studies on the experience of individuals with advanced prostate cancer were typically conducted in primarily White populations participating in randomized controlled trials of disease-directed therapies. With numerous clinical and therapeutic advances for advanced prostate cancer in the past decade, there is a need for a contemporary analysis of the patient experience with a specific focus on identifying unmet needs in Black patients.

In **Chapter 1**, we used data from 701 participants in the International Registry for Men with Advanced Prostate Cancer (IRONMAN) to investigate racial differences in experience with the healthcare system at the time of a new diagnosis of advanced prostate cancer. We estimated prevalence differences by self-reported race for six questions from the Cancer Australia National Cancer Control Indicators about patient information and communication regarding treatment, patient coordination and integration of care, and respect for patient preference. We found that most participants reported a high quality of care, with Black participants generally reporting higher care quality than White participants. Our study suggests that there are other dimensions of the patient experience that are not captured by this survey,

and investigating the interpersonal aspects of care will be important to more fully understand the experience of the healthcare system in this population.

In **Chapter 2**, we used data from 879 IRONMAN participants to investigate racial differences in quality of life at study enrollment and throughout the first year on study. We fit linear mixed effects models of 15 functioning and symptom scales from the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. We found that Black participants tended to have poorer quality of life at study enrollment compared to White participants and that quality of life decreased over the first year on study with minimal differences in trajectory between Black and White participants. Our study identifies domains of quality of life to be further studied and intervened upon to meaningfully improve the overall survivorship experience.

In **Chapter 3**, we used data from 879 IRONMAN participants to investigate racial differences in pain at study enrollment and the association between longitudinal pain trajectories and survival. Participants responded to questions on interference of pain with daily activities, average pain rating, worst pain rating, and presence of bone pain at study enrollment and every 3-6 months throughout up to 5 years of follow up. We fit Cox proportional hazards models and longitudinal survival models to estimate the association between each pain scale and mortality. We found that Black participants had worse pain at enrollment compared to White participants and that higher pain at enrollment and longitudinally for each pain scale was associated with higher mortality after adjusting for measures of disease burden. Our study highlights the need for a deeper understanding of the different facets of pain in advanced prostate cancer populations to determine points for intervention and improvement of quality of life.

Taken together, these studies illuminate the experience of individuals living with advanced prostate cancer. We found numerous quality-of-life detriments in this patient population, especially in Black participants, that can impact both wellbeing and long-term survival from prostate cancer. Using descriptive studies to assess patient experience and quality

of life, this work lays the foundation for further investigation into mechanisms underlying the racial disparities that we identified. This work provides a starting point for patient-centered prostate cancer research to identify ways to improve quality of life and the overall survivorship experience for individuals living with advanced prostate cancer, particularly for Black individuals who face the highest morbidity and mortality from the disease.

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Chapter 1

Experience with the US healthcare system for Black and White patients with advanced prostate cancer

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Abstract

Objective: To assess differences in reported information about treatment, integration into care, and respect by self-identified Black and White individuals with advanced prostate cancer in the US.

Patients and Methods: Prospective cohort study of 701 participants (20% identifying as Black) enrolled in the International Registry for Men with Advanced Prostate Cancer (IRONMAN) at 37 US sites from 2017-2022. Participants were asked six questions from the Cancer Australia National Cancer Control Indicators about their experience with care at study enrollment. Prevalence differences by self-reported race were estimated using marginal standardization of logistic-normal mixed effects models (adjusted for age at enrollment and disease state at enrollment), and 95% confidence intervals (CI) were estimated using parametric bootstrapping.

Results: Most participants reported a high quality of care for each question. Black participants generally reported higher care quality compared to White participants. Black participants reported more frequently that they were offered a written assessment and care plan (71%) compared to White participants (58%, adjusted difference 13 percentage points, 95% CI 4-23). Black participants also reported more frequently being given the name of non-physician personnel who would support them (64%) than White participants (52%, adjusted difference 10, 95% CI 1-20). Prevalence differences did not differ by disease state at enrollment.

Conclusion: Black participants generally reported a higher quality of care compared to White participants. This study calls attention to the need to study potential mediating factors and interpersonal aspects of care in this population to improve survivorship.

Introduction

In the US, Black individuals have a 1.7 times higher incidence of a prostate cancer diagnosis and 2.1 times higher mortality from prostate cancer compared to White individuals.(1) Patients with advanced disease experience the highest prostate cancer morbidity and mortality compared to those with localized disease, and the incidence of advanced disease is highest amongst Black patients.(2) There are two major categories of advanced prostate cancer: metastatic hormone sensitive prostate cancer (mHSPC) and castration resistant prostate cancer (CRPC).(3)

Patient-reported experience with the health care system offers a potential point of intervention for improving equity in survivorship in patients with advanced prostate cancer.(4) Racial disparities persist across a variety of illnesses and healthcare services as a result of patient-level, healthcare systems-level, and care process-level variables.(5) Numerous interventions to move towards equity in treatment have been suggested, such as increasing the diversity of the healthcare workforce, bolstering interpretation services, and using multidisciplinary care teams, among others; many of these interventions have started to be implemented at health care sites across the country and have also shown improved quality of care as a result.(6–8)

Patient experience is a multidimensional construct encapsulating many of these systems- and process-level variables of care as an indicator of health care quality, most often including the areas of information provided about treatment, process of making an appointment, interactions with healthcare professionals, and waiting times.(9) Patient experience is distinct from patient satisfaction: whereas patient experience is typically measured via patient report of what happened (e.g. did you receive information about your treatment?), patient satisfaction is typically measured via patient evaluation and is more influenced by expectations and preferences (e.g. how would you rate the information you received about your treatment?).

Patients undergoing biopsy for suspected prostate cancer want to be thoroughly informed about and have an active role in their care;(10) however, health care professionals often either do not provide full treatment options or side effect profiles to their patients or do not explain them in a way that the patient can understand.(11,12) As domains of patient experience and quality of care have been associated with quality of life and survival in prostate cancer,(4,13,14) research into these patient-reported measures could lead to enhanced prostate cancer survivorship.

Studies on racial disparities in experiences with the health care system among localized prostate cancer survivors are sparse and have shown poorer or similar ratings of communication and involvement in care for Black individuals compared to White individuals.(15, 16) There is a need to describe the experience of individuals with advanced prostate cancer to gather insight into ways to improve care for this population and identify unmet needs.

This study used patient-reported experience measures to examine racial differences in patient experience among people newly diagnosed with advanced prostate cancer in the International Registry for Men with Advanced Prostate Cancer (IRONMAN) study. In this study, we consider race as a social construct that serves as a proxy marker for a range of social experiences shaped by structural racism, and racism is the driver of potential racial disparities, not race itself.(16) We described overall group differences in reported information about treatment, integration into care, and respect for patient preference among IRONMAN participants identifying as Black or White in the US.

Patients and Methods

Study participants

Study participants included individuals with advanced prostate cancer enrolled in the IRONMAN study (NCT 03151629) between July 21, 2017 and October 3, 2022. IRONMAN is a

global prospective cohort of individuals newly diagnosed with advanced prostate cancer (within the past 6 weeks for patients with mHSPC or 3 months for CRPC without a prior diagnosis of mHSPC). Participants are recruited through IRONMAN-affiliated clinicians in 17 countries, and detailed data is collected at study enrollment and throughout a follow-up period of at least 5 years. Because race has different social and historical contexts and categories depending on the country/region and non-US countries in IRONMAN currently have relatively small sample sizes, this analysis focuses on individuals enrolled in the US.

Outcome measure: patient experience

Patient experience was measured using the Cancer Australia National Cancer Control Indicator (NCCI) patient experience items completed by participants at study enrollment via a web-based platform (TrueNth) or paper questionnaires.(17) The NCCI items were adapted from the National Health Service National Cancer Patient Experience Survey (NCPES), the model for further development and refinement of other patient experience measures in countries across the world.(18) IRONMAN includes six of the eight NCCI questions, with two questions on diagnosis removed due to potential confusion between localized and advanced prostate cancer diagnoses amongst the participants. The six questions are rated on a yes/no scale and fall into three categories: patient information and communication regarding treatment (questions 1 and 2); patient coordination and integration of care (questions 3 and 4); and, respect for patient preference (questions 5 and 6).

Demographic and clinical characteristics

Demographic variables (i.e. age at initial prostate cancer diagnosis, age at study enrollment, highest level of education, employment status, marital status, military status, race, ethnicity) were collected through a patient-reported questionnaire at study enrollment. Clinical variables (i.e. disease state at enrollment, Gleason score, prostate-specific antigen (PSA) level, type of health center, baseline treatment) were drawn from patient medical records and entered by study sites.

Race was self-reported by participants at study enrollment, allowing multiple selection from the following categories: White/Caucasian, African/African American/Black/Black British/Caribbean, Asian/Asian American/Asian British, Native Hawaiian or Other Pacific Islander, American Indian/Alaska Native, Middle Eastern, and other. Ethnicity was self-reported by participants choosing between “Hispanic/Latino” and “not Hispanic/Latino” categories. As the IRONMAN population is overwhelmingly not Hispanic/Latino ethnicity, this study focuses specifically on individuals self-identifying as only White or only Black for their race.

Age at study enrollment (years) was included as a continuous variable. Disease state at enrollment was collected at the clinical sites and categorized as mHSPC (do novo metastatic disease at diagnosis or progressed to metastasis during follow up after localized prostate cancer diagnosis) and CRPC (progression of disease while on androgen deprivation therapy or with castrate level of testosterone as determined by the investigator).

Statistical analysis

We summarized demographic and clinical participant characteristics, stratified by self-reported race. We then summarized the proportion of participants, stratified by self-reported race, answering yes or no to each of the six NCCI items.

We fit logistic-normal mixed effects models in the overall population for each NCCI question (both crude models and models adjusted for age at study enrollment and disease state at enrollment) and conducted marginal standardization over the self-reported race variable to obtain adjusted prevalence differences.(19) The outcome for each model was a “yes” response to that NCCI question, and the prevalence difference obtained represents the percent higher prevalence of answering yes to the question for Black participants compared to White participants (controlling for any other variables included in the model). As we were interested in overall differences by self-reported race, we controlled for time-invariant variables (age at study enrollment and disease state at enrollment). We did not control for variables that may mediate the association between self-reported race and care experiences (e.g. education, employment,

insurance status, etc.) in the statistical models.(20) Participants were clustered by study site for each of the models. We then fit the same models stratified by disease state at enrollment (both crude models and models adjusted for age at study enrollment) and by type of health center (NCI-designated center vs. other, crude model only).

To obtain valid standard errors and confidence intervals for our estimates, we used the parametric bootstrap to preserve clustering at study sites.(21) Briefly, rather than resampling observations as in non-parametric bootstrapping, we used the initially fit model to simulate new cluster-specific random effects from the estimated parametric distribution of cluster-specific random effects, and, subsequently, simulated a new binary outcome for each participant. These simulated outcomes and observed covariates were then used in the analysis procedure described above to obtain a bootstrap estimates of prevalence differences. This process was repeated 1,000 times, and 95% confidence intervals were normally approximated by 1.96 standard deviations above and below the prevalence difference estimated from the marginal standardization procedure.

Finally, as an exploratory secondary analysis, we conducted a confirmatory factor analysis using a two-factor and three-factor solution stratified by self-reported race. Additional methods information regarding choice of adjustment variables, the marginal standardization procedure, and the confirmatory factor analysis is available in **Appendix 1**. All analyses were completed using R version 4.1.0.

Patient involvement

An advanced prostate cancer survivor and participant in the IRONMAN study was involved in setting the research question and study design. This individual, along with another prostate cancer survivor who directs a cancer patient advocacy non-profit organization, was also involved in the interpretation of the research findings and review of the manuscript. With the goal of increasing the accessibility of this manuscript to patients and individuals outside of academia, we have included a glossary of technical terms in **Appendix 4**.

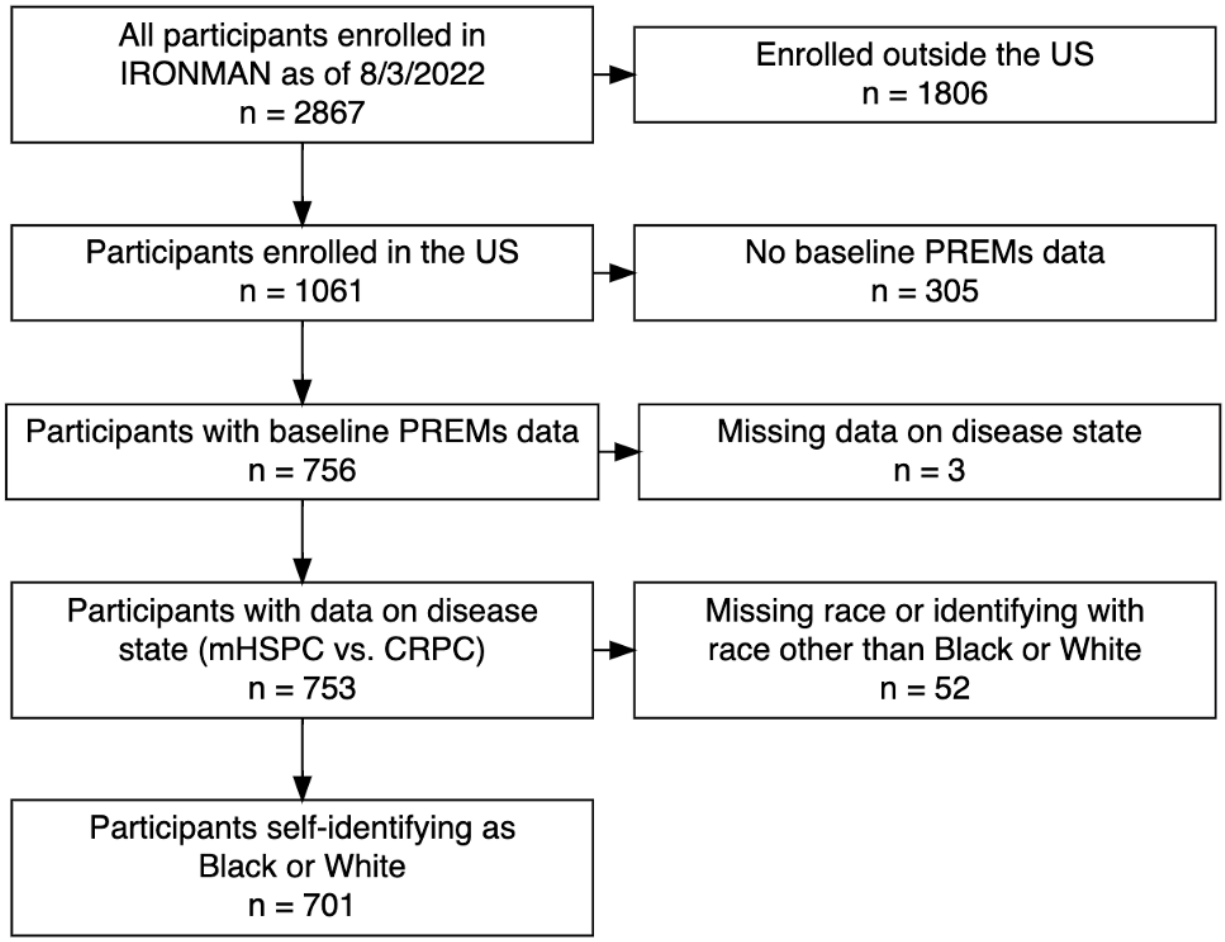
Results

Participant characteristics

This study included 701 participants from IRONMAN self-identifying as White or Black and receiving care at 38 study sites across the US (**Figure 1.1, Table 1.1**). These study sites span academic, private practice, and government health centers and are primarily located in urban centers in regions with high prostate cancer mortality. Demographic and clinical characteristics for the population stratified by self-reported race are shown in **Table 1.2.** The study included 137 participants (20%) identifying as Black and 564 participants (80%) identifying as White. The mean age at enrollment was 69.1 years, and most of the sample (64%) had mHSPC compared to CRPC (36%).

Differences by self-reported race were noted across many of the demographic and clinical characteristics (**Table 1.2**). Black participants were diagnosed with advanced prostate cancer at a younger age, reported considerably lower education, were less likely to be married, were more likely to be disabled, and had higher first on-study PSA levels compared to White participants. No differences by race were noted for disease state at enrollment, military service, or Gleason score.

Figure 1.1. Selection of study participants for analysis of patient-reported experience measures (PREMs)



mHSPC = metastatic hormone-sensitive prostate cancer. CRPC = castration-resistant prostate cancer.

Table 1.1. Sites of enrollment for PREMs study participants by self-reported race (N=38)

	White (N=564)	Black (N=137)
Baylor College of Medicine	6 (1%)	6 (4%)
Chesapeake Urology Associates	5 (1%)	4 (3%)
Columbia University	4 (1%)	2 (1%)
Dana-Farber Cancer Institute	40 (7%)	3 (2%)
Delnor Cancer Center	16 (3%)	1 (1%)
Doylestown Health	14 (2%)	0 (0%)
Duke Cancer Network	5 (1%)	6 (4%)
Duke Comprehensive Cancer Center	44 (8%)	9 (7%)
Durham VA Medical Center	0 (0%)	3 (2%)
Fox Chase Cancer Center - Temple Health	0 (0%)	1 (1%)
Kishwaukee Cancer Center	1 (0%)	0 (0%)
Memorial Sloan Kettering Cancer Center	41 (7%)	7 (5%)
Memphis VA Medical Center	3 (1%)	4 (3%)
Moffitt Cancer Center	2 (0%)	0 (0%)
New York-Presbyterian Brooklyn Methodist Hospital	0 (0%)	1 (1%)
Oregon Health and Sciences Cancer Center	19 (3%)	0 (0%)
Ralph H. Johnson VA Medical Center	9 (2%)	4 (3%)
Reading Health System	9 (2%)	2 (1%)
Robert H. Lurie Comprehensive Cancer Center Northwestern University	4 (1%)	0 (0%)
Roswell Park Cancer Institute	5 (1%)	1 (1%)
Sidney Kimmel Comprehensive Cancer Center	3 (1%)	4 (3%)
Thomas Jefferson University	3 (1%)	1 (1%)
Tulane University	45 (8%)	8 (6%)
University of Alabama-Birmingham	3 (1%)	1 (1%)
University of California Los Angeles	6 (1%)	0 (0%)
University of California San Diego	25 (4%)	0 (0%)
University of Chicago	9 (2%)	7 (5%)
University of Illinois at Chicago	1 (0%)	1 (1%)
University of Michigan	27 (5%)	4 (3%)
University of Mississippi Medical Center	2 (0%)	1 (1%)
University of North Carolina	30 (5%)	7 (5%)

Table 1.1 (continued)

	White (N=564)	Black (N=137)
University of Virginia	86 (15%)	12 (9%)
University of Washington	30 (5%)	1 (1%)
University of Wisconsin	8 (1%)	0 (0%)
Warrenville Cancer Center	1 (0%)	0 (0%)
Wayne St. University Karmanos Cancer Institute	21 (4%)	27 (20%)
Weill Cornell Medical Center	30 (5%)	2 (1%)
Winship Cancer Institute Emory University	7 (1%)	7 (5%)

Table 1.2. Cohort demographics of participants for PREMs analysis by self-reported race (N = 701), IRONMAN Registry 2017-2022

	White (N=564)	Black (N=137)
Age at study entry, years		
Mean (SD)	69.6 (8.9)	67.4 (9.0)
Hispanic/Latino		
No	527 (97%)	121 (96%)
Yes	17 (3%)	5 (4%)
Missing	n = 20	n = 11
Disease state at enrollment		
CRPC	197 (35%)	56 (41%)
mHSPC	367 (65%)	81 (59%)
Highest education level at enrollment		
Less than College	29 (16%)	16 (44%)
Some College or Bachelor's Degree	65 (36%)	11 (31%)
Vocational School/Program	2 (1%)	1 (3%)
Graduate Degree	82 (45%)	7 (19%)
Other	3 (2%)	1 (3%)
Missing	n = 383	n = 101
Marital status at enrollment		
Married	436 (78%)	66 (49%)
In a Civil Partnership	15 (3%)	2 (1%)
Widowed	24 (4%)	11 (8%)
Divorced/Separated	65 (12%)	36 (27%)
Never Married	20 (4%)	19 (14%)
Missing	n = 4	n = 3
Employment status at enrollment		
Retired	332 (59%)	68 (50%)
Working Full-Time	156 (28%)	35 (26%)
Working Part-Time	46 (8%)	8 (6%)
Unemployed	9 (2%)	11 (8%)
Disabled	19 (3%)	13 (10%)
Missing	n = 2	n = 2

Table 1.2 (continued)

	White (N=564)	Black (N=137)
Member of national military at enrollment		
Yes, currently or previously	139 (33%)	30 (29%)
No, I have never served in the national military	286 (67%)	73 (71%)
Missing	n = 139	n = 34
Prostatectomy or biopsy Gleason score		
6 or less	22 (5%)	3 (3%)
7	127 (28%)	35 (33%)
8	85 (19%)	14 (13%)
9-10	222 (49%)	54 (51%)
Missing	n = 108	n = 31
First on-study PSA level (ng/mL)		
Mean (SD)	78.7 (441.0)	176.7 (430.7)
Missing	n = 21	n = 4
Type of health center		
NCI-designated	428 (76%)	106 (77%)
Other academic hospital	95 (17%)	14 (10%)
VA hospital	12 (2%)	11 (8%)
Outpatient clinic	29 (5%)	6 (4%)
Type of therapy at enrollment		
Androgen deprivation therapy (ADT) only	329 (58%)	85 (62%)
Androgen receptor signaling inhibitor (ARSI) only	9 (2%)	5 (4%)
ADT + ARSI only	136 (24%)	25 (18%)
Other	39 (7%)	7 (1%)
No therapy on file within 30 days prior to enrollment	51 (9%)	15 (11%)

mHSPC: metastatic hormone sensitive prostate cancer
CRPC: castration-resistant prostate cancer
PSA: prostate specific antigen

NCCI responses by race

The proportion of participants answering yes or no to each of the six NCCI items is shown in **Table 1.3** stratified by self-reported race. Overall, this population reported receiving high levels of information about their treatments and side effects as well as high levels of involvement in decision-making about their care with the majority of participants answering yes to each of the questions. For example, over 95% of participants were involved as much as they wanted in decisions about their care and had their views taken into account when deciding their treatment plan. For five of the six questions, Black participants had a better experience with care compared to White participants (with minimal difference in the other question).

Table 1.3. Absolute prevalence and prevalence differences (in %) for answering yes to each patient experience measure comparing Black participants to White participants in the IRONMAN cohort

	Absolute prevalence		Prevalence difference (95% CI)	
	White (N=564)	Black (N=137)	Model 1	Model 2
Q1: Have you been offered a written assessment and care plan?	327 (58%)	95 (71%)	13 (4, 23)	13 (4, 23)
Missing	n = 3	n = 3		
Q2: Were you given the name of non-physician personnel who would support you?	292 (52%)	84 (64%)	12 (2, 21)	10 (1, 20)
Missing	n = 4	n = 5		
Q3: Were you involved as much as you wanted to be in decisions about your care?	527 (94%)	129 (96%)	2 (-2, 6)	2 (-2, 6)
Missing	n = 4	n = 3		
Q4: Do you think your views were taken into account when deciding on your treatment plan?	533 (95%)	132 (99%)	2 (0, 5)	2 (0, 5)
Missing	n = 5	n = 3		
Q5: Were treatment side effects explained in a way you could understand?	537 (96%)	127 (94%)	-2 (-6, 2)	-2 (-6, 2)
Missing	n = 5	n = 2		
Q6: Before you started treatment, were you given written information about possible side effects?	483 (86%)	118 (87%)	2 (-5, 8)	1 (-5, 8)
Missing	n = 5	n = 2		

Model 1 is the unadjusted model
Model 2 is adjusted for age at study enrollment (years) and disease state at enrollment (mHSPC vs. CRPC)
CI = confidence interval
Interpretation: Prevalence difference represents the percent higher prevalence of answering yes to the question for Black participants compared to White participants

Differences between Black and White participants

In the overall population of advanced prostate cancer, when adjusted for age at study enrollment and disease state at enrollment, Black participants reported more frequently that they were offered a written assessment and care plan (71%) compared to White participants (58%, adjusted difference 13 percentage points, 95% CI 4-23) (**Table 1.3**). Black participants also reported more frequently being given the name of non-physician personnel who would support them (64%) than White participants (52%, adjusted difference 10, 95% CI 1-20). Black participants in this population also tended to have slightly higher prevalences of being involved as much as they wanted to be in decisions about their care, feeling like their views were taken into account, and receiving written information about side effects compared to White participants, though the differences were small and imprecisely estimated.

In models stratified by disease state at enrollment (mHSPC vs. CRPC, **Table 1.4**) and adjusted for age at study enrollment, Black participants with mHSPC had higher prevalences of being offered a written assessment and care plan (15%; CI 4-27) and having non-physician personnel supporting them (21%; CI 9-33) compared to White participants with mHSPC. Amongst participants with CRPC, no questions reached statistical significance due to a smaller sample size and less variation in the outcomes. In models stratified by type of health center (NCI-designated health center vs. other, **Supplementary Table 1.1**), prevalence differences for each question were larger among non-NCI designated centers with Black participants again reporting better quality of care.

Table 1.4. Prevalence differences (in %) for answering yes to each patient experience measure comparing Black participants to White participants in the IRONMAN cohort, stratified by disease state at enrollment

	mHSPC Model 1	***mHSPC Model 2***	***CRPC Model 1***	***CRPC Model 2***
Question	*PD (95% CI)*	*PD (95% CI)*	*PD (95% CI)*	*PD (95% CI)*
Question 1 (N_m=447, N_c=248)	16 (4, 27)	15 (4, 27)	11 (-4, 26)	11 (-4, 26)
Question 2 (N_m=443, N_c=249)	22 (10, 33)	21 (9, 33)	-6 (-23, 11)	-6 (-23, 11)
Question 3 (N_m=442, N_c=252)	5 (0, 9)	4 (0, 9)	-1 (-6, 4)	-1 (-6, 4)
Question 4 (N_m=441, N_c=252)	2 (-2, 6)	2 (-2, 6)	---[a]	---[a]
Question 5 (N_m=443, N_c=251)	0 (-4, 4)	0 (-5, 4)	-5 (-13, 3)	-5 (-13, 3)
Question 6 (N_m=443, N_c=251)	5 (-2, 12)	5 (-3, 12)	-4 (-15, 6)	-5 (-16, 7)

Model 1 is the unadjusted model
Model 2 is adjusted for age at study enrollment (years)
N_m is the N for that question in the subset of patients with mHSPC (metastatic hormone sensitive prostate cancer)
N_c is the N for that question in the subset of patients with CRPC (castration-resistant prostate cancer)
PD = prevalence difference; CI = confidence interval
Interpretation: PD represents the percent higher prevalence of answering yes to the question for Black participants compared to White participants

[a] PD could not be estimated as some simulated outcomes had no variability and models could not be fit

Discussion and Conclusion

Discussion

Our study expands the understanding of patient experience with the health care system amongst individuals with advanced prostate cancer who experience the highest morbidity and mortality compared to those with localized disease. In a nationwide population of 701 individuals with advanced prostate cancer in the US, we found that this group reports high levels of information about their treatment and potential side effects, and that they were involved in decision-making processes around their care.

For most questions, participants identifying as Black reported higher prevalences of information about treatment, integration in care, and respect for patient preference compared to White participants. Participants in our study received care at 38 institutions in the US, and we did not find evidence to suggest that large differences at only a few institutions are driving these results.

Compared to previous literature, these results were unexpected. The existing literature focused on individuals with localized disease receiving care from surgeons and urologists; as medical oncologists are the primary physicians caring for IRONMAN participants, it is possible that this discrepancy with previous literature results from different care practices and patterns by physician specialty. Additionally, previous literature utilized different and more narrow outcome measures, restricting the domains of patient experience that could be explored.

The reasons as to why Black participants reported being provided more information about treatment and non-physician care personnel compared to White participants in our study are unclear. Some explanations could include IRONMAN study sites intentionally implementing interventions to decrease racial disparities in care in line with recent recommendations,(22) that higher education in White participants allows for more careful scrutiny of provided paperwork and the care team, or that individuals who are eligible to enrolled in IRONMAN but decline are different than those who consent to the study. Type of health center likely plays a central role in

mediating the relationship between race and patient experience with White participants having poorer experience with care at non-NCI designated centers in this population. Our results demonstrate that patient experience is a complex phenomenon; further investigation into potential mediating factors is needed to determine best practices for ensuring that all patients receive appropriate care.

The patient experience measures assessed in this study can be thought of as indicators of quality of care regarding provision of information and interactions with healthcare professionals. The measures in this study, however, do not assess the more humanistic perceptions and ratings of the patient's care. While the responses to these questions are mostly "yes," this does not necessarily translate into experiences of being treated with courtesy and respect. Racism permeates through the US medical system, leading to poorer quality of care and ratings of interpersonal treatment for non-White individuals.(23) Patient satisfaction has been shown to be associated with long-term quality of life and survival in a variety of cancers including prostate cancer.(24,25) To better understand racial disparities in care experiences amongst patients with advanced prostate cancer, it will be important to study patient satisfaction and the more interpersonal aspects of care. A number of instruments covering these aspects of care have been developed for this purpose.(27,28,29) Additionally, since race is a proxy for lived social experiences, it is important to note that these outcomes can change over a person's life course as a result of shifting social hierarchies.

In our analyses, we assessed each question individually. As many patient experience and satisfaction instruments use a summary score, we conducted an exploratory analysis to determine if the NCCI instrument could be reduced and used in a similar way. We conducted two confirmatory factor analyses: one using the three domains outlined by Cancer Australia and one using two domains identified in a previous validation study(27) of the instrument in White patients (**Supplementary Table 1.2**). We found that the two- and three-factor solutions both perform well in White participants; however, both models fit poorly in Black participants. As there

was so little variability in outcomes for Black participants, this was expected. The results of this factor analysis suggest against reducing this instrument from the individual six questions in Black patient populations, and they also emphasize the importance of using additional measures (such as patient satisfaction as described above) to identify issues not captured by this instrument that are more relevant to this population.

There are several potential limitations of this study. First, this study focuses specifically on participants self-identifying their race as either Black or White. As a previous study has shown additional differences in patient experience for Asian Americans and Latinx populations,(28) it is important to expand this research amongst more diverse populations. Secondly, as mentioned above, the instrument used in this study does not capture patient satisfaction and the more interpersonal aspects of care. Additional measures will need to be used in this population to obtain a fuller picture of the experience of patients with advanced prostate cancer. Finally, these results may not be generalizable to other health centers. Centers participating in IRONMAN tend to be highly-resourced which could lead to better experience with care; other health spaces with fewer resources (such as rural and primary health centers or urban centers with less clinical trial infrastructure) likely have different distributions of patient experience.

With 38 study sites across the US, IRONMAN captures the major sites at which patients receive care for advanced prostate cancer, and our study expands the research of patient experience into this population that experiences high morbidity and mortality. Overall, our findings of disparate experiences of care call attention to the importance of studying patient experience with the health care system amongst patients with advanced prostate cancer. Our results also highlight the importance of considering additional metrics of patient experience within and outside of the healthcare system that may influence disease trajectories in this population to improve quality of care and increase prostate cancer survival.

Conclusion

Patients with prostate cancer desire an active role in their care.(10) While it has been shown that health care professionals often do not engage patients in core shared decision-making processes for those with localized disease,(11) the results of this study show that participants with newly diagnosed advanced prostate cancer in the IRONMAN registry generally feel like they have the information they need and are included appropriately in decisions about their care. In this population, participants identifying as Black have more positive experiences with information about treatments, integration into care, and respect for patient preference compared to White participants. This study provides novel information into the experience of patients with advanced prostate cancer in the US and calls attention to the need to study potential mediating factors and interpersonal aspects of care in this population to improve survivorship.

Chapter 2

Quality of life in the year after new diagnosis with advanced prostate cancer for Black and White individuals living in the US

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Abstract

PURPOSE: To assess differences in baseline and longitudinal quality of life among self-identified Black and White individuals in the US with advanced prostate cancer.

PATIENTS AND METHODS: Prospective cohort of individuals enrolled in the International Registry for Men with Advanced Prostate Cancer (IRONMAN) from 2017-2023. Participants newly diagnosed with metastatic hormone sensitive (mHSPC) or castration resistant (CRPC) prostate cancer were administered the EORTC QLQ-C30 Quality of Life (QoL) Survey at study enrollment and every three months thereafter for up to one year of follow-up. Individual questions were categorized into 100-point scales for functioning (N=6 domains) and symptom status (N=9 domains). Linear mixed effects models were fit for each of the scales (adjusted for age at enrollment and disease state at enrollment), and estimated coefficients (mean, 95% CI) were used to determine racial differences at baseline and in longitudinal QoL trajectories.

RESULTS: The cohort included 879 individuals (20% identifying as Black) enrolled at 38 US sites. Compared to White participants at baseline, Black participants had worse constipation (mean 6.3 percentage points higher; 95% CI 2.9-9.8), financial insecurity (5.7 (1.4-10.0)), and pain (5.1 (0.9-9.3)). Quality of life decreased over time in the first year with minimal differences in trajectory between Black and White participants. Most notably, role functioning decreased by 0.7 percentage points (95% CI -0.8, -0.5) per month, and fatigue worsened by 0.6 percentage points (95% CI 0.5, 0.7) per month.

CONCLUSION: There are notable differences in quality of life at diagnosis of mHSPC or CRPC for Black and White individuals, and quality of life declines similarly in the first year for both groups. Interventions that address specific aspects of quality of life in these patients could meaningfully improve the overall survivorship experience.

Introduction

In the US, Black individuals have a 1.7 times higher incidence and 2.1 times higher mortality from prostate cancer compared to White individuals.(1) Patients with advanced disease experience the highest prostate cancer-associated morbidity and mortality compared to those with localized disease, and the incidence of advanced disease is highest amongst Black patients.(2) There are two major categories of advanced prostate cancer: metastatic hormone sensitive prostate cancer (mHSPC) and castration resistant prostate cancer (CRPC).(3)

Quality of life (QoL) is a multidimensional construct that comprises several aspects of the human experience including health and psychological status, independence, social relationships, environment, and personal beliefs. Integration of patient-reported outcome measures of QoL into routine oncology care represents a potential point for intervention to improve survivorship and decrease disparities in prostate cancer populations. In a randomized trial of individuals with metastatic solid tumors, the group assigned to complete electronic patient-reported symptom measures with notifications sent to the care team for severe/worsening symptoms had a median overall survival time that was 20% longer than the control group.(29) Further, a 10-point increase in global QoL (on a scale of 0 to 100) on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was associated with a 17% lower risk of death in a population of 1,097 prostate cancer patients with primarily localized disease.(30)

Studies of QoL in patients with advanced prostate cancer have traditionally investigated the relationship between a specific disease-directed treatment in a clinical trial and QoL with few non-White participants. Observational studies similarly suffer from a lack of racial diversity. A study of 280 White patients with advanced prostate cancer across 7 countries in 2007 found a steady decline in QoL over the first year after study enrollment.(31) A more recent study of 81 White individuals with locally advanced or advanced prostate cancer in 2017 found that QoL fluctuates over the five years following diagnosis with sexual concerns remaining consistently

high.(32) There is a need for a contemporary analysis of QoL in a population that more accurately represents the diversity of prostate cancer patients and their survivorship experience.

This study used patient-reported measures to examine racial differences in QoL among individuals newly diagnosed with mHSPC or CRPC in the International Registry for Men with Advanced Prostate Cancer (IRONMAN). We assessed differences in baseline QoL and longitudinal QoL at 3-month intervals over the first year after diagnosis with mHSPC or CRPC. We described overall group differences in functional status and symptom domains of QoL among IRONMAN participants identifying as Black or White in the US.

Patients and Methods

Study participants

Study participants included individuals newly diagnosed with mHSPC or CRPC enrolled in the IRONMAN registry (NCT 03151629) between July 21, 2017 and January 23, 2023. IRONMAN is a global prospective cohort of individuals diagnosed with advanced prostate cancer in the three months prior to enrollment (with no more than 90 days of systemic therapy for CRPC prior to enrollment for patients with CRPC and no more than 90 days of active therapy for patients with mHSPC). Participants are recruited through IRONMAN-affiliated clinicians in 16 countries, and detailed data is collected at study enrollment and throughout a follow-up period of at least 5 years.(33) Study sites span academic, private practice, and government health centers and are primarily located in urban centers in regions with high prostate cancer mortality. Because race has different social and historical contexts with different categories in different global regions, and because non-US countries in IRONMAN currently have relatively small sample sizes, this analysis focuses on individuals enrolled in the US.

Outcome measure: Quality of life (EORTC QLQ-C30 version 3)

QoL was measured with version 3 of the EORTC QLQ-C30 over a period of up to 12 months, with assessments performed at study enrollment and 3, 6, 9, and 12 months. Surveys

were self-administered using a web-based platform (TrueNth) or paper questionnaires.(34) The EORTC QLQ-C30 survey consists of 2 questions on global health status (1-7 Likert scale, “very poor” to “excellent”), 15 questions on functional status (1-4 Likert scale, “not at all” to “very much”), and 13 questions on symptom status (1-4 Likert scale, “not at all” to “very much”). The 30 questions are combined and linearly transformed to 15 scale scores with a range of 0 to 100. The instrument covers 5 functional scales (physical, role, emotional, cognitive, and social) with higher scale scores representing better functioning in the domain. In addition, nine symptom scales were assessed (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with higher scale scores representing more severe symptoms. The EORTC QLQ-C30 questionnaire has shown high construct validity and good reliability in a population of cancer patients and a racially diverse population over the age of 50 years with similar factor structures by race.(35,36) A study of EORTC outcomes in prostate cancer patients estimated clinically meaningful changes in scale scores to be between 5 and 10 percentage points on the 100-point scales;(37) Prior to February 20, 2020, IRONMAN participants could complete the questionnaire two weeks before or after the target date; this was subsequently adjusted to be +/- three months of the target date to improve study feasibility.

Demographic and clinical characteristics

Demographic information (age, highest level of education, employment status, marital status, military status, race, ethnicity) was collected through a patient-reported questionnaire at study enrollment. Clinical variables (disease state at enrollment, Gleason score, prostate-specific antigen (PSA) level, treatment at baseline, metastatic status at baseline, and type of health center) were abstracted from patient medical records and entered by study sites.

Race was self-reported by participants at study enrollment, allowing multiple selection from the following categories: White/Caucasian, African/African American/Black/Black British/Caribbean, Asian/Asian American/Asian British, Native Hawaiian or Other Pacific Islander, American Indian/Alaska Native, Middle Eastern, and other. Ethnicity was self-reported

by participants choosing between “Hispanic/Latino” and “not Hispanic/Latino” categories. As the IRONMAN population enrolled at the time of this study was overwhelmingly not Hispanic/Latino ethnicity and there was insufficient power to study other racial groups, this study focuses specifically on individuals self-identifying their race as only Black or White.

Age at study enrollment (years) was included as a continuous variable. Disease state at enrollment was categorized as mHSPC (*de novo* metastatic disease at diagnosis or progressed to metastasis after localized prostate cancer diagnosis) and m0 or m1 CRPC (progression of disease while on androgen deprivation therapy or with castrate level of testosterone as determined by the investigator).

Statistical analysis

We summarized demographic and clinical participant characteristics, stratified by self-reported race. We calculated the 15 EORTC scale scores for each individual at each time point if the questionnaire and all required questions for each scale were complete.(38) Missing individual covariates and EORTC scale scores on completed questionnaires were imputed using multiple imputation by chained equations (MICE)(39) with the data in wide format. Scale scores in which the entire questionnaire was missing were temporarily given a value of -250 as a numerical, proxy missing indicator to ensure that these scores would not be imputed. MICE was conducted using classification and regression trees with 10 iterations for each of 10 imputations and with the scale scores constrained between 0 and 100 (inclusive of the bounds). Subsequently, scale scores for missing questionnaires were re-marked as missing. Sensitivity analyses were conducted with different values for the missing indicator.

Longitudinal missingness in questionnaires was assessed, and an in-depth description of missing data exploration is included in **Appendix 2.** As no clear patterns of reasons for missing whole questionnaires arose from these analyses, we fit linear mixed effects models for each of the fifteen scale scores with timepoints clustered within participant who were then clustered within study site. Initial models only included only race, month of follow-up

questionnaire time point (continuous), and their interaction, assuming a linear relationship between the outcome scale and time. As we were interested in overall differences by self-reported race, adjusted models additionally controlled for time-invariant variables (age at study enrollment and disease state at enrollment). We did not control for variables that may mediate the association between self-reported race and QoL (e.g. employment, marital status, etc.) in the statistical models.(20) Baseline differences and differences in longitudinal trajectories in each scale by race were estimated and pooled using Rubin's Rules.(40) A sensitivity analysis excluding individuals who were censored due to being off-study was conducted. Figures depicting these trajectories by race using model coefficients were created to visualize trends. The longitudinal analyses were additionally stratified by disease state at enrollment to determine differences for participants with mHSPC and CRPC.

Additional methods information regarding choice of adjustment variables, missing data exploration, and the longitudinal analysis is available as supplementary material accompanying the online article. All analyses were completed using R version 4.1.0 with statistical significance assessed at the 0.05 level.

Patient involvement

An advanced prostate cancer survivor and participant in the IRONMAN study was involved in setting the research question, study design, interpretation of the research findings, and review of the manuscript. With the goal of increasing the accessibility of this manuscript to patients and individuals outside of academia, we have included a glossary of technical terms in **Appendix 4**.

Results

Participant characteristics

This study included 879 participants from IRONMAN self-identifying as White (N=704, 80%) or Black (N=175, 20%); participants received care at 38 study sites across the US (**Supplementary Figure 2.1, Supplementary Table 2.1**). Demographic and clinical characteristics for the sample, stratified by self-reported race, are shown in **Table 2.1.** For the entire cohort, the mean age at enrollment was 69.1 years with a standard deviation of 8.9 years, and most of the participants (65.2%) had mHSPC compared to CRPC (34.8%).

Differences by self-reported race were noted across many of the demographic and clinical characteristics (**Table 2.1**). Black participants were diagnosed with advanced prostate cancer at a younger age, reported lower education, were less likely to be married, were more likely to be disabled, had higher first on-study PSA levels, and had a shorter time on study on average compared to White participants. The most commonly received therapies at any point between three months prior to and 12 months after enrollment were androgen deprivation therapy (88.9%), androgen receptor signaling inhibitors (61.7%), and chemotherapy (17.5%) (**Supplementary Table 2.2**).

Table 2.1. Cohort demographics of participants for quality-of-life analysis by self-reported race (N = 879), IRONMAN Registry 2017-2023

	White (N=704)	Black (N=175)
Age at study entry, years		
Mean (SD)	69.5 (9.0)	67.2 (8.7)
Hispanic/Latino		
No	657 (97%)	156 (96%)
Yes	22 (3%)	6 (4%)
Missing	n = 25	n = 13
Disease state at enrollment		
CRPC	241 (34%)	65 (37%)
mHSPC	463 (66%)	110 (63%)
Highest education level at enrollment		
Less than College	29 (14%)	18 (43%)
Some College or Bachelor's Degree	72 (35%)	13 (31%)
Vocational School/Program	2 (1%)	1 (2%)
Graduate Degree	101 (49%)	9 (21%)
Other	3 (1%)	1 (2%)
Missing	n = 497	n = 133
Marital status at enrollment		
Married	545 (78%)	88 (51%)
In a Civil Partnership	20 (3%)	2 (1%)
Widowed	29 (4%)	12 (7%)
Divorced/Separated	76 (11%)	43 (25%)
Never Married	28 (4%)	26 (15%)
Missing	n = 6	n = 4
Employment status at enrollment		
Retired	408 (58%)	82 (48%)
Working Full-Time	200 (29%)	45 (26%)
Working Part-Time	58 (8%)	11 (6%)
Unemployed	12 (2%)	16 (9%)
Disabled	22 (3%)	17 (10%)
Missing	n = 4	n = 4

Table 2.1 (continued)

	White (N=704)	Black (N=175)
Member of national military at enrollment		
Yes, currently or previously	182 (33%)	37 (28%)
No, I have never served in the national military	364 (67%)	97 (72%)
Missing	n = 158	n = 41
Prostatectomy or biopsy Gleason score		
6 or less	26 (5%)	3 (2%)
7	163 (28%)	45 (34%)
8	106 (18%)	20 (15%)
9-10	278 (49%)	63 (48%)
Missing	n = 131	n = 44
First on-study PSA level (ng/mL)		
Mean (SD)	88.6 (484.8)	156.9 (396.3)
Missing	n = 33	n = 8
Metastases at baseline		
No	65 (9%)	12 (7%)
Yes	639 (91%)	163 (93%)
Type of health center		
Clinic	30 (4%)	7 (4%)
Hospital	125 (18%)	21 (12%)
NCI-designated	535 (76%)	131 (75%)
VA	14 (2%)	16 (9%)
Time on study (months)		
Mean (SD)	28.9 (17.4)	24.8 (17.2)

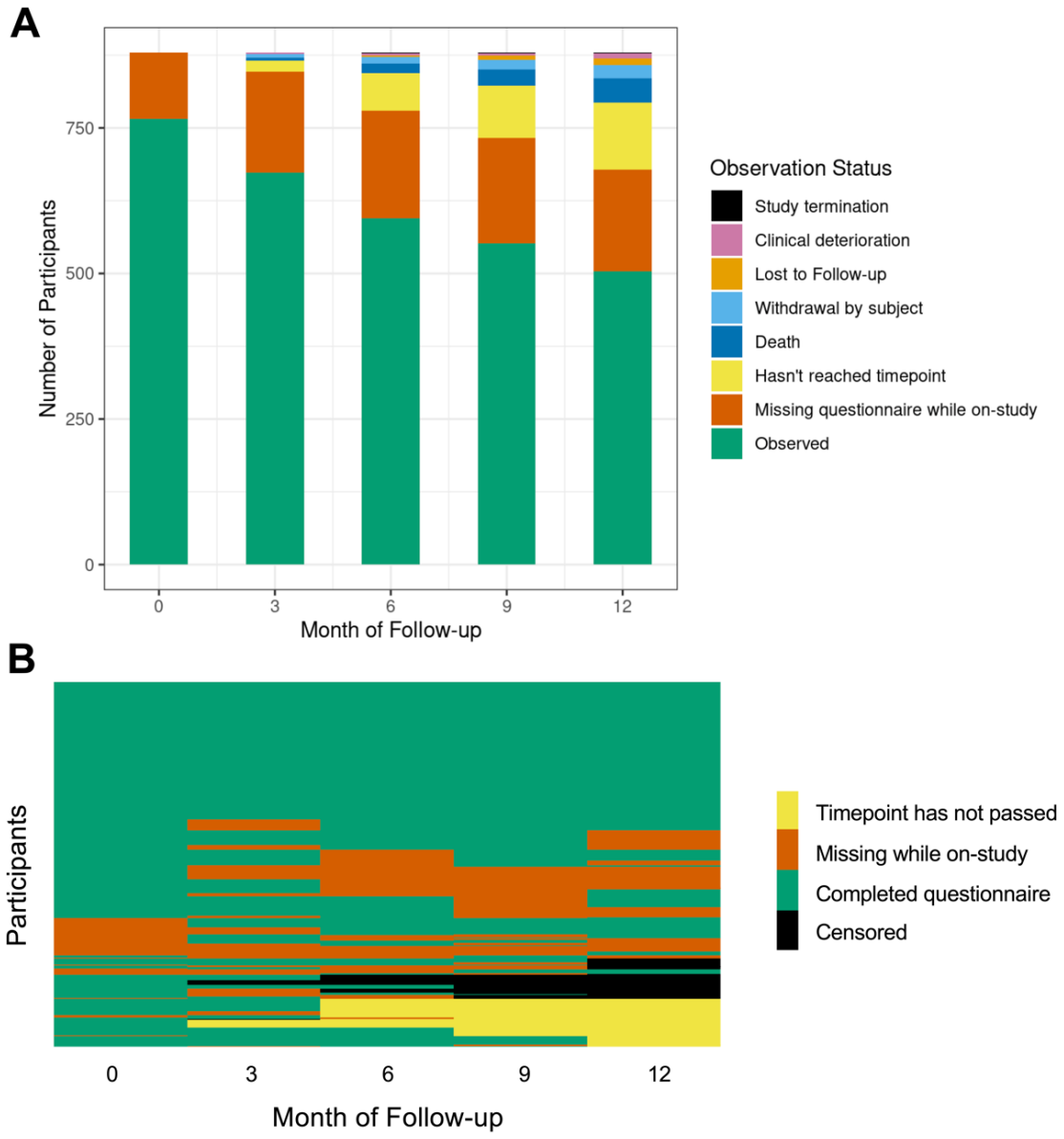
mHSPC = metastatic hormone-sensitive prostate cancer
CRPC = castration resistant prostate cancer
PSA = prostate-specific antigen

Overview of missing data

Visualization of longitudinal missing questionnaires is shown in **Figure 2.1**. The proportion of participants completing questionnaires, missing questionnaires, or being off-study is represented in **Figure 2.1A**. Eighty-seven percent of participants completed the baseline questionnaire, declining to 74% completion by individuals on-study at month 12. Over the 12-month period, 790 individuals (90%) remained on-study.

The longitudinal missing data patterns for full questionnaires are depicted in **Figure 2.1B.** Thirty-nine percent of participants completed questionnaires at all five timepoints. The remainder of study participants exhibited 30 distinct missing non-monotone data patterns.

Figure 2.1. Overview of longitudinal missing patient-reported questionnaires for study participants in the first year after enrollment
Figure 2.1A: Proportion of questionnaire completeness and reasons for incompleteness at each timepoint. **Figure 2.1B**: Longitudinal completion of questionnaires for each participant (N=897).



Baseline differences in QoL by race

Baseline results from the longitudinal analyses are shown in **Table 2.2.** Overall, participants tended to have high functioning and low symptom burden across each of the scales. White participants had mean functioning scales of 80-85 (on a scale of 0-100; higher score is indicative of higher QoL) at the baseline questionnaire; mean symptom scales for White participants were at or below 30 (on a scale of 0-100; lower score is indicative of a higher QoL). The most disruptive symptoms for White participants were sleep problems (mean 30.3, 95% CI 27.6, 33.0) and fatigue (mean 30.1, 95% CI 27.7, 32.6).

Compared to White participants, Black participants reported several differences in QoL domains at baseline. Black participants had better emotional functioning (comprising questions about anxious and depressive symptoms) at baseline (increase of mean 4.4 percentage points, 95% CI 1.4, 7.5) compared to White participants. However, Black participants reported worse pain (5.1 point increase, 95% CI 0.9, 9.3) and financial insecurity (7.0 point increase, 95% CI 2.7, 11.4) compared to White participants. Scale scores varied substantially more between participants than between study sites.

Table 2.2: EORTC QLQ-C30 quality of life scale scores at study enrollment for White and Black participants (N = 879)

	Score for White participants Mean (95% CI), N = 704	Difference for Black participants Mean (95% CI), N = 175[a]		Standard deviation of participant random effect	Standard deviation of site random effect
		UNADJUSTED	ADJUSTED		
Global QoL (QL)[1]	70.9 (68.8, 73.0)	-0.6 (-4.0, 2.9)	-0.7 (-4.2, 2.8)	15.4	3.3
Functioning Scales[1]					
Physical (PF)	84.1 (81.6, 86.6)	-1.0 (-4.3, 2.3)	-2.0 (-5.2, 1.2)	15.0	4.9
Emotional (EF)	81.3 (79.3, 83.1)	**4.4 (1.4, 7.5)**	**5.0 (2.0, 8.0)**	13.6	3.0
Social (SF)	80.5 (78.1, 83.0)	0.7 (-3.1, 4.6)	0.9 (-3.0, 4.7)	16.3	4.6
Role (RF)	80.4 (77.7, 83.2)	-0.2 (-4.6, 4.2)	-0.5 (-4.9, 3.9)	18.7	5.0
Cognitive (CF)	84.2 (82.3, 86.2)	0.5 (-2.5, 3.6)	0.4 (-2.6, 3.5)	13.8	3.5
Symptom Scales[2]					
Fatigue (FA)	30.1 (27.7, 32.6)	-1.8 (-5.7, 2.0)	-1.8 (-5.7, 2.1)	17.3	4.5
Nausea/vomiting (NV)	4.1 (3.3, 4.9)	**2.8 (1.0, 4.6)**	**2.4 (0.6, 4.1)**	7.1	0.2
Pain (PA)	19.0 (16.4, 21.6)	**5.1 (0.9, 9.3)**	**4.5 (0.3, 8.6)**	18.3	4.9
Dyspnea (DY)	13.8 (11.7, 15.9)	0.6 (-3.2, 4.4)	1.2 (-2.7, 5.0)	17.4	2.9
Sleep (SL)	30.3 (27.6, 33.0)	**-7.3 (-11.9, -2.7)**	**-7.9 (-12.5, -3.3)**	20.0	3.7
Appetite (AP)	10.7 (8.8, 12.6)	2.3 (-1.1, 5.7)	2.2 (-1.2, 5.6)	13.9	2.8
Constipation (CO)	12.3 (10.6, 14.0)	**6.0 (2.5, 9.5)**	**6.3 (2.9, 9.8)**	14.5	1.4
Diarrhea (DI)	10.3 (8.5, 12.1)	-1.4 (-4.4, 1.6)	-1.7 (-4.7, 1.3)	11.4	3.1
Financial insecurity (FI)	16.4 (13.8, 19.0)	**7.0 (2.7, 11.4)**	**5.7 (1.4, 10.0)**	20.2	4.2

Bolded represents statistical significance at the 0.05 level.

Unadjusted model includes race as the only covariate. Adjusted model additionally includes age and disease state (mHSPC or CRPC) at study enrollment.

All scale scores are rated on a scale of 0-100; [1]a higher score is indicative of higher quality of life for the global and functioning scales, [2]while a lower score is indicative of a higher quality of life for the symptom scales.

[a] Interpretation: mean change in EORTC scale score at enrollment for Black participants compared to White participants. For the global and functioning scales, a positive number represents higher quality of life for Black participants compared to White participants. For the symptom scales, a positive number represents lower quality of life for Black participants compared to White participants.

Longitudinal differences in QoL by race

Trajectory results from the longitudinal analyses are provided in **Table 2.3**, with a graphical representation provided in **Figure 2.2**. For the majority of scales, White participants showed a decline in QoL over time. Role functioning (the ability to accomplish daily activities) declined most sharply of the functioning scales, with scores for White participants losing 0.7 percentage points on average per month (95% CI -0.8, -0.5). Fatigue worsened most sharply of the symptom scales, with scores for White participants gaining 0.6 percentage points on average per month (95% CI 0.5, 0.7); pain also worsened over time (mean 0.4, 95% CI 0.2, 0.6).

Overall, in this cohort, Black and White participants have similar trajectories in QoL over their first year after enrollment for the vast majority of symptom and functioning scales. In a few scales, Black participants had slower decline or faster improvement compared White participants. Most notably, reported financial security for Black participants improved by an additional 0.6 percentage points per month compared to White participants (95% CI -0.8, -0.4). The results for both baseline and longitudinal differences in the scale scores were robust to sensitivity analyses with different values for the missing indicator in the MICE procedure **(Supplementary Table 2.3)** as well as when individuals who were off study at any point in the first year were excluded **(Supplementary Table 2.4)**. When stratified by disease state at study enrollment, results were largely the same across participants with mHSPC and CRPC (**Supplementary Table 2.5 and 2.6)**.

Table 2.3: Longitudinal changes in EORTC QLQ-C30 scales per month for White and Black participants during the first year after study enrollment (N = 879)

	Change per month for White participants[a] Mean (95% CI), N = 704		Additional change for Black participants[b] Mean (95% CI), N = 175	
	UNADJUSTED	**ADJUSTED**	**UNADJUSTED**	**ADJUSTED**
Global QoL (QL) [1]	**-0.4 (-0.5, -0.2)**	**-0.4 (-0.5, -0.2)**	0.1 (-0.2, 0.4)	-0.1 (-0.2, 0.1)
Functioning Scales[1]				
Physical (PF)	**-0.6 (-0.7, -0.5)**	**-0.6 (-0.7, -0.5)**	0.1 (-0.1, 0.4)	**-0.4 (-0.5, -0.3)**
Emotional (EF)	-0.1 (-0.2, 0)	-0.1 (-0.2, 0)	0.1 (-0.2, 0.4)	**0.3 (0.2, 0.4)**
Social (SF)	**-0.3 (-0.4, -0.1)**	**-0.3 (-0.4, -0.1)**	0.1 (-0.3, 0.5)	0.1 (-0.1, 0.2)
Role (RF)	**-0.7 (-0.8, -0.5)**	**-0.6 (-0.8, -0.5)**	0.3 (-0.1, 0.7)	-0.1 (-0.3, 0)
Cognitive (CF)	**-0.3 (-0.5, -0.2)**	**-0.3 (-0.5, -0.2)**	0.3 (0, 0.7)	0 (-0.1, 0.1)
Symptom Scales[2]				
Fatigue (FA)	**0.6 (0.5, 0.7)**	**0.6 (0.5, 0.7)**	**-0.5 (-0.9, -0.2)**	0 (-0.1, 0.2)
Nausea/vomiting (NV)	0 (-0.1, 0.1)	0 (-0.1, 0.1)	-0.1 (-0.3, 0.1)	**-0.2 (-0.2, -0.1)**
Pain (PA)	**0.4 (0.2, 0.6)**	**0.4 (0.2, 0.6)**	-0.2 (-0.6, 0.2)	**-0.3 (-0.4, -0.1)**
Dyspnea (DY)	**0.6 (0.4, 0.7)**	**0.6 (0.4, 0.7)**	-0.1 (-0.4, 0.3)	0.2 (0, 0.3)
Sleep (SL)	0.1 (-0.1, 0.3)	0.1 (-0.1, 0.3)	0.2 (-0.3, 0.6)	**-0.3 (-0.5, -0.2)**
Appetite (AP)	0.1 (-0.1, 0.2)	0 (-0.1, 0.2)	0 (-0.4, 0.4)	0 (-0.1, 0.1)
Constipation (CO)	**0.2 (0.1, 0.4)**	**0.2 (0.1, 0.4)**	-0.3 (-0.7, 0.1)	0.1 (0, 0.2)
Diarrhea (DI)	0.1 (0, 0.2)	0.1 (-0.1, 0.2)	-0.1 (-0.5, 0.2)	-0.1 (-0.2, 0)
Financial insecurity (FI)	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0)	-0.2 (-0.6, 0.2)	**-0.6 (-0.8, -0.4)**

Bolded represents statistical significance at the 0.05 level.

Unadjusted model includes race as the only covariate. Adjusted model additionally includes age and disease state (mHSPC or CRPC) at study enrollment.

All scale scores are rated on a scale of 0-100; [1]a higher score is indicative of higher quality of life for the global and functioning scales, [2]while a lower score is indicative of a higher quality of life for the symptom scales.

[a] Interpretation: the mean change in EORTC scale score per month for White participants. For the global and functioning scales, a positive number represents an increase in quality of life over time. For the symptom scales, a positive number represents a decrease in quality of life over time.

[b] Interpretation: the mean additional change in EORTC scale score per month for Black participants compared to White participants. Adding this number to the change in score per month for White participants gives the change in score per month for Black participants.

Figure 2.2: Longitudinal trajectories in EORTC QLQ-C30 scale scores for study participants in their first year after enrollment (N = 15 scales).

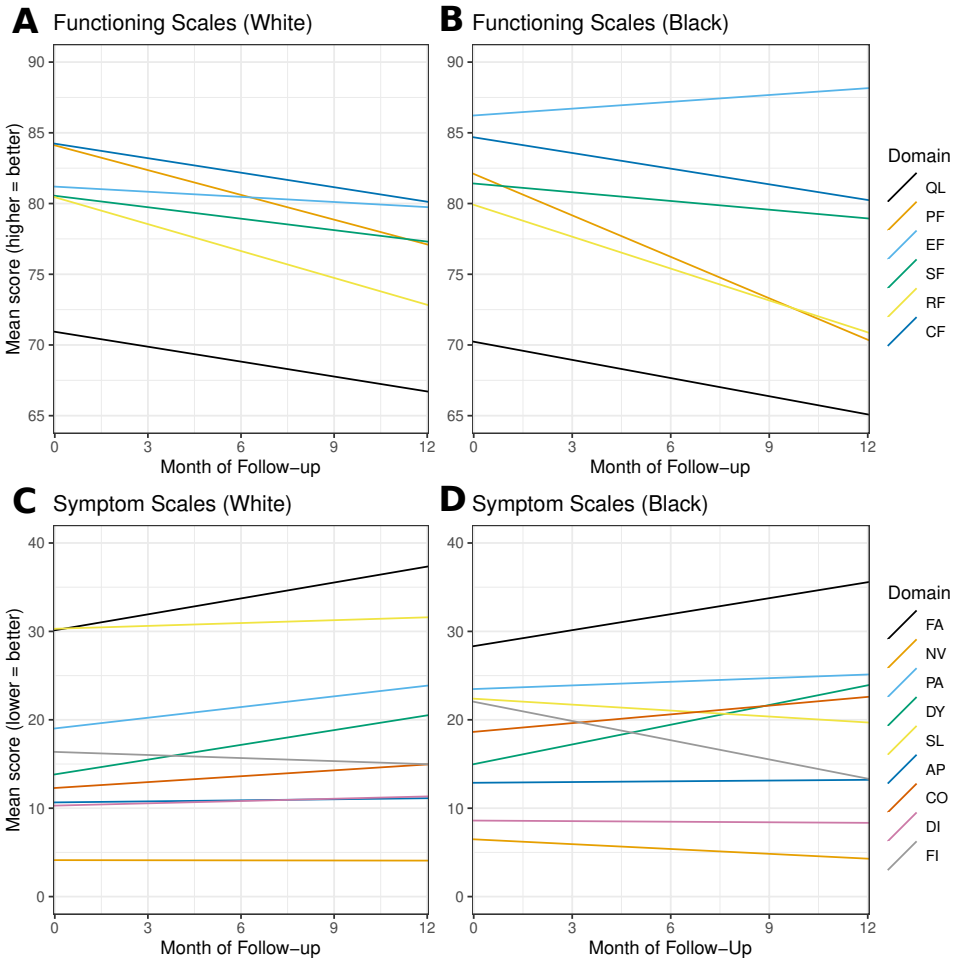


Figure 2.2A: Trajectories of functioning scales for White participants. Figure 2.2B: Trajectories of functioning scales for Black participants. Figure 2.2C: Trajectories of symptom scales for White participants. Figure 2.2D: Trajectories of symptom scales for Black participants. QL = global quality of life, PF = physical functioning, EF = emotional functioning, SF = social functioning, RF = role functioning, CF = cognitive function, FA = fatigue, NV = nausea/vomiting, PA = pain, DY = dyspnea, SL = sleep, AP = appetite, CO = constipation, DI = diarrhea, FI = financial insecurity

Discussion

Our study expands the understanding of QoL in prostate cancer survivors into those with advanced disease, with a particular focus on differences in QoL by self-reported race. In a nationwide sample of 879 individuals with advanced prostate cancer in the US participating in the IRONMAN registry, we found that individuals tend to report good QoL in their first year of study. Our IRONMAN study population had slightly better functioning and fewer symptoms at study enrollment compared to the EORTC recurrent/metastatic prostate cancer reference population.(41)

At study enrollment, Black and White participants reported a number of differences in QoL. Black participants reported higher emotional functioning and better sleep quality compared to White participants, but worse pain, constipation, and financial security. Some previous studies in populations with localized prostate cancer suggested that Black individuals have poorer QoL in all domains at baseline compared to White individuals,(42,43) while others reported similar QoL across domains by race(44,45) or higher QoL in Black individuals.(46–48) Two of many possible explanations for Black participants reporting better emotional functioning than White participants are differences in cultural stigma around mental health by race and the role of religion in coping with illness.(49,50)

Longitudinally, QoL generally declined for both Black and White participants in our study during their first year after enrollment in IRONMAN. This was true for both the participants with mHSPC as well as those with CRPC, suggesting that the decline in QoL over time isn't only due to treatment side effect, cancer-related symptoms, or disease progression. This is in line with previous studies of individuals with advanced prostate cancer showing declines or stability in QoL in White individuals.(31,32) A monthly change of approximately 0.4 percentage points per month in our study correlates to the clinically meaningful change of 5 percentage points in a year described in a recent study,(37) demonstrating that the majority of statistically significant

changes that we find in QoL over time are also clinically meaningful for the participant and their cancer care.

Many factors can mediate or modify the association between race and QoL in patients with prostate cancer and are worth investigating in future studies for potential points of intervention. One such potential mediator is therapy received. Multiple randomized controlled trials in advanced prostate cancer populations have shown changes in QoL after treatment with various therapies for advanced prostate cancer;(51–54) however, these trials had small sample sizes and were not racially diverse. Other potential mediators are social factors that differ by race such as access to social determinants of health resources that support a nutritious diet, physical activity and dietary supplements, quiet living spaces to support high quality sleep, and access to healthcare resources to decrease treatment side effects, among others.(55) One potential effect modifier is genetic ancestry: though genetic ancestry is correlated with self-reported race, they do not perfectly overlap.(56) Genetic ancestry and single nucleotide polymorphisms have been shown to be associated with prostate cancer initiation and progression which could also impact the more biological symptom scales like pain.(57,58) Our study lays the foundation for future studies to investigate the mechanisms underlying differences in QoL seen here.

There are several potential limitations of this study. First, this study focuses specifically on participants self-identifying their race as either Black or White; it is important to expand this research amongst more diverse populations. Second, the EORTC QLQ-C30 questionnaire has not specifically been validated in this study population, though prostate cancer and PROMs experts determined that the EORTC questionnaire is a reasonable and useful instrument to assess general QoL in patients with advanced prostate cancer. Moreover, the majority of scales have shown high reliability in a racially diverse population over the age of 50 years with similar factor structures in Black and White individuals that reflect our study population.(59,60) Finally, these results may not be generalizable to individuals who choose not to participate in IRONMAN

or individuals receiving care at other health centers within or outside of the US. Centers participating in IRONMAN tend to be highly-resourced and located in urban environments; individuals living in more rural areas of the US or receiving care at urban centers with less clinical trial infrastructure could have different distributions and trajectories of QoL.

Our study expands the research of QoL into a diverse population of individuals newly diagnosed with advanced prostate cancer using a questionnaire that has been validated in racially diverse populations. The differences identified in QoL subdomains at the time of a new advanced prostate cancer diagnosis for Black and White individuals, in addition to declines in QoL over time for both groups, highlight an opportunity for further investigation into potential interventions to improve the prostate cancer survivorship experience and improve survival overall for this patient population.

Acknowledgments

The authors would like to thank the participants enrolled in the IRONMAN registry, without whom this research would not be possible. We would also like to thank the IRONMAN investigators and study teams at the 38 sites included in this study for their efforts to enroll and support the IRONMAN participants.

Chapter 3

Racial disparities in pain and survival for Black and White individuals with advanced prostate cancer in the US

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Abstract

Objective: To investigate racial differences in multiple patient-reported dimensions of pain and the association between baseline and longitudinal pain and mortality among individuals in the US with newly diagnosed advanced prostate cancer.

Patients and methods: Prospective cohort study of individuals with newly diagnosed metastatic hormone sensitive (mHSPC) or castration resistant (CRPC) enrolled in the International Registry for Men with Advanced Prostate Cancer (IRONMAN) from 2017-2023 at US sites. Participants were administered five questions on pain at study enrollment and during up to 5 years of follow up. Differences in pain scores at study enrollment by race were investigated. Cox proportional hazards models and joint longitudinal survival models were fit for each of the scale scores to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for the association with all-cause mortality.

Results: The cohort included 879 individuals (20% self-identifying as Black) enrolled at 38 US sites. Black participants had worse pain at baseline compared to White participants, most notably a higher average pain rating (mean 3.1 vs 2.2 on a 10-point scale). For each of the pain scales, higher pain at baseline was associated with higher mortality after adjusting for measures of disease burden; this was most pronounced for patients reporting severe bone pain at baseline compared to no pain at all (HR of 2.47; 95% CI 1.44, 4.22). The association between pain and mortality was stronger for participants with CRPC compared to mHSPC and when accounting for longitudinal pain trajectories.

Conclusion: Black participants reported worse pain than White participants, and more severe pain was associated with higher mortality independent of clinical covariates for all pain scales. Future studies should investigate the different facets of pain in this population to determine the factors upon which to intervene to improve quality of life and survivorship, particularly for Black individuals.

Introduction

In the US, an estimated 120,000 individuals are living with advanced prostate cancer,(61) defined as metastatic hormone sensitive prostate cancer (mHSPC) or castration resistant prostate cancer (CRPC).(3) Black individuals experience the most significant advanced prostate cancer burden with over double the age-adjusted prevalence and mortality compared to White individuals.(61)

An important quality of life detriment experienced by many individuals with advanced prostate cancer is pain, often driven by metastasis to the bone.(62) In addition to bone pain, other types of pain, including neuropathic, osteoarthritic, and muscular pain, are frequently experienced as chronic pain with poorly-managed breakthrough episodes.(63) Pain is a subjective experience shaped by cultural and individual expectations in addition to exacerbating factors such as psychosocial stressors, medical comorbidities, and ability to navigate the health system.(64) Additionally, individual and systemic discrimination lead to health professionals prescribing analgesics less frequently to Black and Hispanic patients with cancer compared to White patients.(65) Previous studies have shown that Black individuals with advanced prostate cancer report more severe bone pain compared to White individuals,(66,67) and pain typically increases for this population towards the end of life.(68)

Increased pain has been shown to be associated with worse survival in advanced prostate cancer populations;(69–72) however, most studies were conducted in primarily White populations participating in randomized controlled trials of disease-directed therapies. A study of 599 participants in three phase III trials for advanced prostate cancer therapies found that higher pain on the Wisconsin Brief Pain Inventory (BPI) was associated with a 43% higher risk of mortality.(69) A study of 1125 participants in the LATITUDE trial randomizing androgen deprivation therapy (ADT) with and without abiraterone acetate additionally found that higher pain on the BPI was associated with poorer survival after accounting for longitudinal trajectories in pain.(70)

There is a need for a more contemporary and comprehensive analysis of racial disparities in multiple dimensions of pain and survival in individuals with advanced prostate cancer given numerous therapeutic advances in the past two decades. This analysis expands this area of research to assess racial differences in multiple patient-reported dimensions of pain and the association between baseline and longitudinal pain and mortality among individuals newly diagnosed with mHSPC or CRPC in the International Registry for Men with Advanced Prostate Cancer (IRONMAN).

Patients and Methods

Study participants

Study participants included individuals newly diagnosed with mHSPC or CRPC who enrolled in the IRONMAN registry (NCT 03151629) between July 21, 2017 and January 23, 2023. IRONMAN is an international prospective cohort of individuals with no more than 90 days of life-prolonging therapy prior to enrollment for patients with CRPC and no more than 90 days of active therapy including ADT for patients with mHSPC. Participants are recruited through IRONMAN-affiliated clinicians in 16 countries.(33) Study sites are primarily located in urban centers in regions with high prostate cancer mortality. This analysis focused on individuals enrolled in the US.

Exposure measures: Pain

Pain was self-reported by study participants at enrollment and every 3-6 months throughout a follow-up period of up to 5 years.(33) The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) contains two questions on the presence and interference of pain rated on a Likert scale of 1 (“not at all”) to 4 (“very much”). These two questions are combined and linearly transformed to a pain scale score with a range of 0 (least severe) to 100 (most severe).(38) The minimally important difference (MID) for deterioration on the EORTC pain scale for individuals with prostate cancer is five

points.(37) The EORTC QLQ-C30 pain scale has shown high reliability (Cronbach's alpha 0.83) in a racially diverse population over the age of 50 years.(36)

The Brief Pain Inventory (BPI) contains two questions on severity of average and worst pain in the past 24 hours rated on a scale of 1 ("no pain") to 10 ("pain as bad as you can imagine"). The MID for deterioration on the BPI scale is between 1.3 and 1.6 points.(73) The BPI has shown high construct validity in a racially diverse population and high concordance with other pain scales in an advanced prostate cancer population.(74,75)

The Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index (FACT-FPSI) contains one question on presence of bone pain in the past week rated on a Likert scale of 0 ("not at all") to 4 ("very much"). While the MID and reliability/validity for the bone pain question have not specifically been investigated, these have been assessed for the overall FACT-FPSI scale in prostate cancer patients.(76,77)

Demographic and clinical characteristics

Demographic information (age, highest level of education, employment status, marital status, military status, race, ethnicity) was collected through patient-reported questionnaires at study enrollment. Clinical variables (disease state at enrollment, Gleason score, first on-study prostate-specific antigen (PSA) level, treatments received prior to study and throughout follow-up, metastatic status at baseline, *de novo* metastases at baseline, sites of metastases at baseline, and type of health center) were abstracted from patient medical records and entered by study sites at the time of enrollment. Disease state was categorized as mHSPC (*de novo* metastatic disease at diagnosis or progressed to metastasis after localized prostate cancer diagnosis) and M0 or M1 CRPC (progression of disease while on ADT or with castrate level of testosterone as determined by the investigator).

Statistical analysis

We summarized demographic and clinical variables stratified by pain interference at study enrollment. Next, we investigated racial differences in the four pain scales at enrollment

by comparing average scores and creating histograms of all scores. We calculated the Pearson correlation between each of the pain scales to investigate whether the different scales measure different aspects of pain.

Second, we defined the time to all-cause mortality as the time from the date of study enrollment to the date of death and constructed Kaplan-Meier estimates of the survivor function to visualize differences by race, disease state, and pain scale score categories. We created three categories of pain for each pain scale corresponding to no pain, a little/light pain, and moderate-to-severe pain. We estimated 80^{th} percentile survival and 95% confidence intervals (CIs) for each category of pain at study enrollment; due to short follow-up for many participants, we were not able to estimate median overall survival.

Third, we fit separate Cox proportional hazards models using the imputed datasets to investigate the association between each of the four pain scales at enrollment and all-cause mortality. Missing individual covariates and pain scale scores on completed questionnaires were imputed using multiple imputation by chained equations (MICE).(39) An in-depth description of missing data exploration and methods is included in **Appendix 3**. All Cox models were adjusted for potential clinical confounders including age at study enrollment (continuous), first PSA on study (continuous), Gleason score (categorical; 6 or less, 7, 8, or 9-10), disease state at enrollment (mHSPC or CRPC), metastatic status at baseline (yes/no), de novo metastatic status at enrollment (yes/no), and site of metastases at baseline (categorical; none, lymph node only, bone and/or lymph node only, liver/lung metastases present, or other). Participants were clustered by site ID (N=38) with robust standard errors, and the baseline hazard was stratified by year of enrollment. Hazard ratios (HRs) and 95% CIs were estimated and pooled across imputed datasets using Rubin's Rules.(40) Analyses were additionally stratified by disease state at enrollment and race.

Finally, to investigate the association between longitudinal pain score trajectories throughout follow-up and mortality, we fit joint longitudinal survival models.(78) Linear mixed

effects models for the pain scales were fit with month of questionnaire as linear, quadratic, and cubic terms and with observations clustered within study participants. Each linear mixed effects model was jointly modeled with the same Cox models described above using the JM package in R, assuming a Weibull baseline hazard.(79) Results were pooled across imputed datasets, and HRs and 95% CIs for the association between the time-varying pain scale scores and mortality were estimated. The association between bone pain and mortality was not assessed due to incompatibility of categorical longitudinal outcomes with joint modeling capabilities in the JM package. All analyses were completed using R version 4.1.0 with statistical significance assessed at the 0.05 level.

An advanced prostate cancer survivor is an author on this paper, and a glossary of technical terms is included in **Appendix 4** for increased accessibility to non-academic audiences.

Results

Participant characteristics

This analysis included 879 participants from IRONMAN self-identifying as White (N = 704, 80%) or Black (N = 175, 20%) who received care at 38 study sites across the US (**Supplementary Figure 3.1, Supplementary Table 3.1**). Demographic and clinical characteristics stratified by level of pain interference are shown in **Table 3.1.** For the entire cohort, the mean age at enrollment was 69.1 (standard deviation 8.9 years), and a larger portion of the participants (65%) had mHSPC at enrollment compared to CRPC (35%). The most commonly received therapies at any point on study were ADT (89%), androgen receptor signaling inhibitors (ARSIs) (67%), and chemotherapy (24%) (**Supplementary Table 3.2**).

Table 3.1: Cohort demographic and clinical characteristics by interference of pain with daily activities at baseline (N = 879), IRONMAN Registry 2017-2023

	No interference (N=484)	At least some interference (N=273)	Missing (N=122)
Age at study entry, years			
Mean (SD)	69.8 (8.8)	68.3 (9.2)	67.7 (8.7)
Self-reported race			
White	397 (82%)	208 (76%)	99 (81%)
Black	87 (18%)	65 (24%)	23 (19%)
Hispanic/Latino			
No	451 (97%)	245 (96%)	117 (98%)
Yes	16 (3%)	10 (4%)	2 (2%)
Missing	n = 17	n = 18	n = 3
Disease state at enrollment			
mHSPC	318 (66%)	170 (62%)	85 (70%)
mCRPC	149 (31%)	91 (33%)	33 (27%)
nmCRPC	17 (4%)	12 (4%)	4 (3%)
Highest education level at enrollment			
Less than College	26 (17%)	21 (29%)	0 (0%)
Some College or Bachelor's Degree	53 (34%)	26 (36%)	6 (30%)
Vocational School/Program	2 (1%)	1 (1%)	0 (0%)
Graduate Degree	73 (46%)	23 (32%)	14 (70%)
Other	3 (2%)	1 (1%)	0 (0%)
Missing	n = 327	n = 201	n = 102
Marital status at enrollment			
Married	355 (74%)	186 (69%)	92 (77%)
In a Civil Partnership	11 (2%)	8 (3%)	3 (3%)
Widowed	26 (5%)	11 (4%)	4 (3%)
Divorced/Separated	67 (14%)	43 (16%)	9 (8%)
Never Married	21 (4%)	22 (8%)	11 (9%)
Missing	n = 4	n = 3	n = 3
Employment status at enrollment			
Retired	281 (58%)	150 (55%)	59 (50%)
Working Full-Time	146 (30%)	58 (21%)	41 (35%)
Working Part-Time	37 (8%)	21 (8%)	11 (9%)
Unemployed	12 (2%)	13 (5%)	3 (3%)

	No interference (N=484)	At least some interference (N=273)	Missing (N=122)
Disabled	6 (1%)	29 (11%)	4 (3%)
Missing	n = 2	n = 2	n = 4
Member of national military at enrollment			
Yes, currently or previously	109 (30%)	77 (36%)	33 (31%)
No, I have never served in the national military	252 (70%)	137 (64%)	72 (69%)
Missing	n = 123	n = 59	n = 17
Prostatectomy or biopsy Gleason grade			
6 or less	20 (5%)	5 (2%)	4 (4%)
7	118 (30%)	58 (27%)	32 (31%)
8	70 (18%)	36 (17%)	20 (19%)
9-10	182 (47%)	112 (53%)	47 (46%)
Missing	n = 94	n = 62	n = 19
First on-study PSA level (ng/mL)			
Mean (SD)	82.5 (409.9)	114.8 (456.5)	152.0 (672.1)
Missing	n = 23	n = 13	n = 5
De novo metastatic disease at enrollment			
Yes	198 (67%)	111 (70%)	55 (75%)
No	99 (33%)	48 (30%)	18 (25%)
Missing	n = 187	n = 114	n = 49
Location of metastases at enrollment			
No metastases at baseline	17 (6%)	12 (7%)	4 (7%)
Lymph nodes only	35 (13%)	13 (7%)	3 (5%)
Bone +/- lymph nodes only	168 (61%)	119 (68%)	35 (64%)
Other soft tissue metastases present	56 (20%)	32 (18%)	13 (24%)
Missing	n = 208	n = 97	n = 67
Type of health center			
Clinic	22 (5%)	13 (5%)	2 (2%)
Hospital	90 (19%)	34 (12%)	22 (18%)
NCI	359 (74%)	209 (77%)	98 (80%)
VA	13 (3%)	17 (6%)	0 (0%)
Time on study (months)			
Mean (SD)	29.6 (17.3)	24.2 (17.6)	30.7 (16.4)

mHSPC = metastatic hormone-sensitive prostate cancer
CRPC = castration resistant prostate cancer
PSA = prostate-specific antigen

Differences by interference of pain at study enrollment were noted across many of the demographic and clinical characteristics (**Table 3.1**). While more than half of participants reported no pain interference, 36% of those completing the baseline questionnaire reported at least some pain interference. Participants with at least some interference of pain were diagnosed with advanced prostate cancer at a younger age, were more likely to be Black, reported lower education, had higher first on-study PSA levels, and had a shorter time on-study on average compared to participants with no pain interference.

Baseline differences in pain by self-reported race

At study enrollment, Black participants reported more severe pain on average across all pain scales compared to White participants with the exception of bone pain, where no differences by race were seen (**Table 3.2**). Racial differences in each pain scale were similar for both participants with mHSPC and CRPC; for example, White participants with mHSPC had a mean EORTC pain scale score of 19.1 compared to the mean of 26.7 for Black participants with mHSPC. The scale scores for participants with CRPC were similar (mean 18.4 for White participants and 26.2 for Black participants).

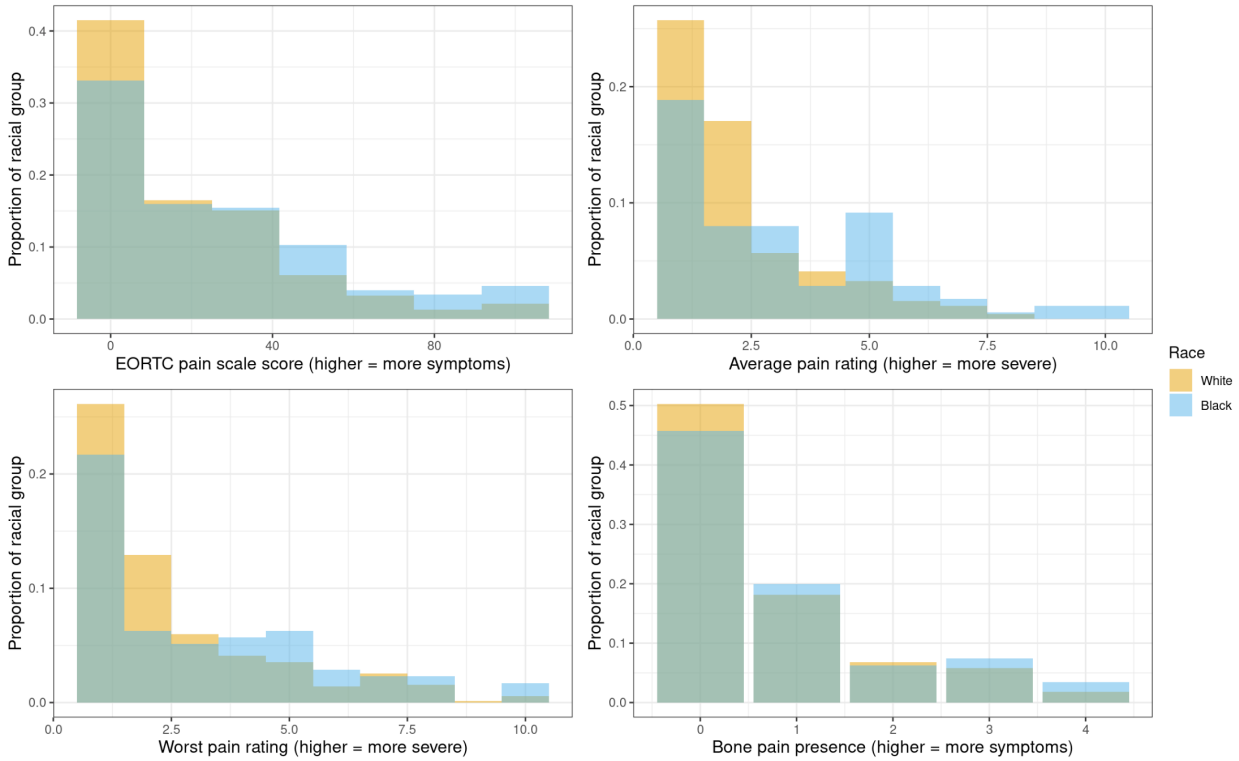
Table 3.2: Average pain at study enrollment by disease state at enrollment and self-reported race (N = 4 pain scales)

	CRPC		mHSPC	
	White (N=241)	**Black (N=65)**	**White (N=463)**	**Black (N=110)**
EORTC pain scale (0-100)[a]				
Mean (SD)	18.4 (23.1)	26.2 (28.1)	19.1 (25.0)	26.7 (30.0)
Missing	n = 33	n = 4	n = 67	n = 19
Q1: How often have you had pain in the past week?				
1 - Not at all	108 (51%)	23 (38%)	200 (51%)	38 (41%)
2 - A little	77 (37%)	25 (41%)	138 (35%)	33 (36%)
3 - Quite a bit	18 (9%)	8 (13%)	42 (11%)	12 (13%)
4 - Very much	7 (3%)	5 (8%)	16 (4%)	9 (10%)
Missing	n = 31	n = 4	n = 67	n = 18
Q2: How often did pain interfere with your daily activities in the past week?				
1 - Not at all	132 (63%)	34 (56%)	265 (67%)	53 (58%)
2 - A little	58 (28%)	17 (28%)	96 (24%)	22 (24%)
3 - Quite a bit	15 (7%)	7 (11%)	20 (5%)	8 (9%)
4 - Very much	3 (1%)	3 (5%)	16 (4%)	8 (9%)
Missing	n = 33	n = 4	n = 66	n = 19
Rate your average pain (1-10)				
Mean (SD)	2.2 (1.6)	3.1 (2.2)	2.2 (1.6)	3.2 (2.4)
Missing	n = 42	n = 10	n = 73	n = 19
Rate your pain at its worst in the last 24 hours (1-10)				
4 or greater	48 (24%)	18 (33%)	85 (22%)	37 (41%)
Less than 4	151 (76%)	37 (67%)	305 (78%)	54 (59%)
Missing	n = 42	n = 10	n = 73	n = 19
How often have you had bone pain in the past week?				
0 - Not at all	120 (60%)	31 (55%)	234 (61%)	49 (55%)
1 - A little bit	42 (21%)	14 (25%)	86 (22%)	21 (24%)
2 - Somewhat	21 (11%)	6 (11%)	27 (7%)	5 (6%)
3 - Quite a bit	10 (5%)	4 (7%)	31 (8%)	9 (10%)
4 - Very much	6 (3%)	1 (2%)	7 (2%)	5 (6%)
Missing	n = 42	n = 9	n = 78	n = 21

[a] The EORTC pain scale score is created through a linear transformation of Q1 and Q2 below

Though the largest proportion of participants reported no pain at baseline across each of the four pain scales, the majority of study participants reported at least some pain on each of the scales, with Black participants tending to report more severe pain (**Figure 3.1**). Clinical disease characteristics were similar by race with the exception of a higher PSA level in Black participants compared to White participants (**Supplementary Table 3.3)**. The four pain scales have moderate-to-high correlation with each other (correlation coefficient between 0.56 and 0.87) (**Supplementary Table 3.4**).

Figure 3.1: Distributions of pain at study enrollment by self-reported race

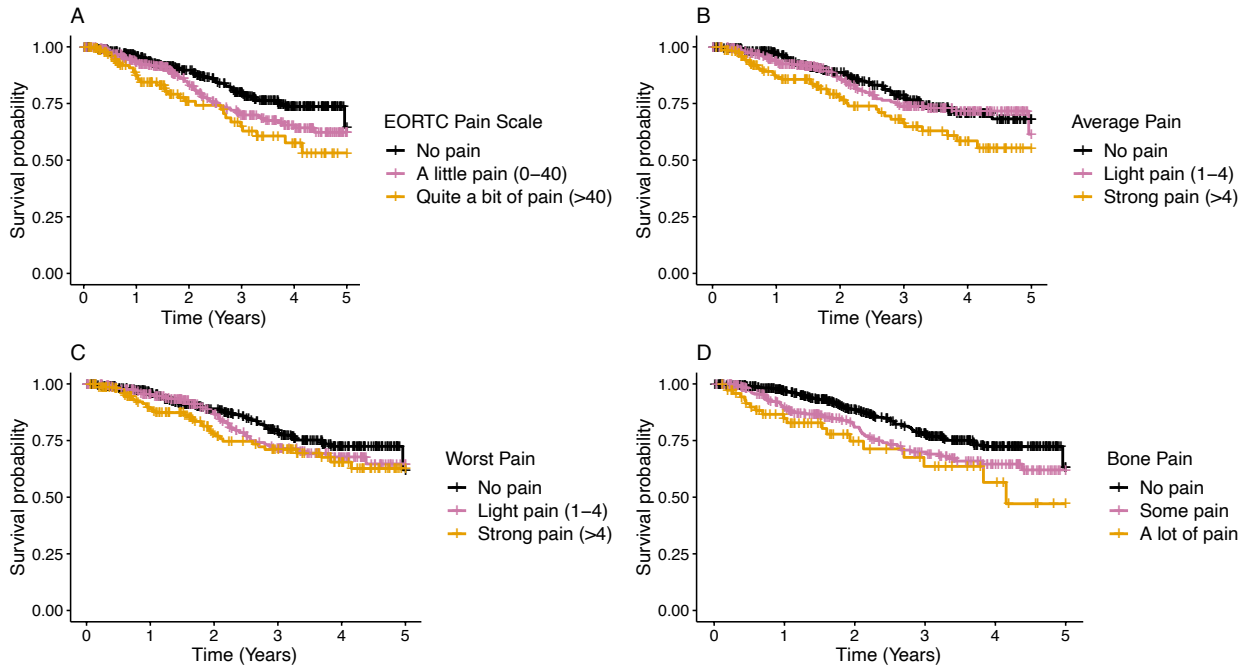


Differences in survival time by self-reported race, disease state, and baseline pain

The median follow-up time for White participants in the study was 2.24 years compared to 1.73 years for Black participants with 137 (19.5%) White participants and 37 (21.4%) Black participants dying throughout follow-up (**Supplementary Table 3.5**). The 80th percentile survival for White participants was 2.57 years (95% CI 2.34, 2.95) and for Black participants was 2.09 years (95% CI 1.68, 2.98) (**Supplementary Figure 3.2**). The 80th percentile survival for participants with mHSPC was 2.84 years (95% CI 2.57, 3.83) and for participants with CRPC was 2.08 years (95% CI 1.75, 2.40) (**Supplementary Figure 3.3**).

The 80th percentile survival for participants experiencing the highest amounts of pain at enrollment was substantially lower than the 80th percentile survival for participants experiencing no pain at enrollment for all four pain scales (**Figure 3.2, Supplementary Table 3.6**). For example, the 80th percentile survival for participants reporting a score of more than 40 on the EORTC pain scale at baseline was 1.60 years (95% CI 0.99, 2.66) compared to 3.01 years (95% CI 2.50, 3.83) for participants with no pain on the EORTC scale at baseline.

Figure 3.2: Kaplan-Meier curves for overall survival by pain categories at study enrollment, IRONMAN Registry 2017-2023



Association between pain and all-cause mortality

For all four pain scales, more frequent or severe pain at study enrollment was associated with an increased risk of all-cause mortality (**Table 3.3**). Most notably, compared to participants with no bone pain, participants with a lot of bone pain at baseline had an adjusted hazard ratio for death of 2.47 (95% CI 1.44, 4.22).

Table 3.3: Hazard ratios (HR) and 95% confidence intervals (CI) for the association between baseline and longitudinal pain scales and death, IRONMAN Registry 2017-2023 (N=879)

		Pain at enrollment		**Longitudinal pain**	
Pain scale	**Comparison**	Age-only model HR (95% CI)	Fully-adjusted model[a] HR (95% CI)	Age-only model HR (95% CI)	Fully-adjusted model[a] HR (95% CI)
EORTC scale	10-points on 0-100 scale	1.12 (1.06, 1.17)	1.10 (1.03, 1.17)	1.30 (1.20, 1.42)	1.29 (1.19, 1.40)
Average pain	1 point on 1-10 scale	1.22 (1.10, 1.35)	1.19 (1.08, 1.32)	1.34 (1.21, 1.48)	1.32 (1.20, 1.46)
Worst pain	1 point on 1-10 scale	1.17 (1.08, 1.26)	1.16 (1.08, 1.25)	1.31 (0.90, 1.91)[b]	1.31 (1.20, 1.43)
Bone pain	Some vs. none	1.62 (1.12, 2.33)	1.61 (1.10, 2.37)	--[c]	--[c]
Bone pain	A lot vs. none	2.70 (1.65, 4.42)	2.47 (1.44, 4.22)	--[c]	--[c]

[a] Cox model for pain and death adjusted for age at enrollment, first prostate-specific antigen (PSA) level on-study, Gleason score, disease state at enrollment, metastatic status at baseline, de novo metastatic disease at baseline, and sites of metastases at baseline
[b] Standard error is inflated as all imputed datasets led to Hessian matrices that were not positive definite for the worst pain scale
[c] Longitudinal models for bone pain not fit because categorical outcomes are currently incompatible with joint longitudinal survival model capabilities in JM R package

The association between pain and all-cause mortality was stronger for participants with CRPC compared to those with mHSPC and was similar among Black and White participants (**Table 3.4**).

Table 3.4: Stratified analyses for the association between pain scales at enrollment and death, IRONMAN Registry 2017-2023

		mHSPC (N = 573)		CRPC (N = 306)	
Pain scale	**Comparison**	Age-only model HR (95% CI)	Fully-adjusted model[a] HR (95% CI)	Age-only model HR (95% CI)	Fully-adjusted model[a] HR (95% CI)
EORTC scale	10-points on 0-100 scale	1.08 (1.00, 1.17)	1.08 (0.99, 1.18)	1.15 (1.06, 1.24)	1.12 (1.03, 1.22)
Average pain	1 point on 1-10 scale	1.14 (0.99, 1.30)	1.12 (0.97, 1.30)	1.31 (1.11, 1.54)	1.25 (1.06, 1.47)
Worst pain	1 point on 1-10 scale	1.12 (1.02, 1.24)	1.13 (1.01, 1.26)	1.21 (1.07, 1.38)	1.18 (1.05, 1.32)
Bone pain	Some vs. none	1.02 (0.57, 1.83)	0.98 (0.54, 1.79)	2.54 (1.69, 3.81)	2.43 (1.56, 3.79)
Bone pain	A lot vs. none	2.48 (1.11, 5.52)	2.22 (0.99, 4.98)	3.19 (1.22, 8.32)	3.01 (1.00, 9.06)
		White (N = 704)		**Black (N = 175)**	
Pain scale	**Comparison**	Age-only model HR (95% CI)	Fully-adjusted model[b] HR (95% CI)	Age-only model HR (95% CI)	Fully-adjusted model[b] HR (95% CI)
EORTC scale	10-points on 0-100 scale	1.11 (1.04, 1.18)	1.10 (1.02, 1.18)	1.11 (1.04, 1.19)	1.09 (0.98, 1.21)
Average pain	1 point on 1-10 scale	1.21 (1.07, 1.37)	1.20 (1.04, 1.37)	1.25 (1.11, 1.40)	1.24 (1.06, 1.44)
Worst pain	1 point on 1-10 scale	1.14 (1.04, 1.25)	1.14 (1.04, 1.25)	1.26 (1.11, 1.42)	1.27 (1.05, 1.53)
Bone pain	Some vs. none	1.56 (1.05, 2.32)	1.53 (1.02, 2.29)	1.64 (0.59, 4.50)	2.85 (0.73, 11.15)
Bone pain	A lot vs. none	2.76 (1.64, 4.64)	2.56 (1.47, 4.46)	2.61 (0.88, 7.80)	3.57 (1.02, 12.55)

[a] Cox model for pain and death adjusted for age at enrollment, first prostate-specific antigen (PSA) level on-study, Gleason score, metastatic status at baseline, *de novo* metastases at baseline, and sites of metastases at baseline

[b] Cox model for pain and death adjusted for age at enrollment, first prostate-specific antigen (PSA) level on-study, Gleason score, disease state at enrollment, metastatic status at baseline, *de novo* metastases at baseline, and sites of metastases at baseline

For the EORTC pain scale, average pain rating, and worst pain rating, more frequent or severe pain longitudinally was associated with an increased risk of mortality (**Table 3.3**). A one-point increase in average pain severity was associated with a 34% higher hazard of mortality (95% CI 1.21, 1.48). In the longitudinal survival models, the association between more frequent or severe pain and risk of death was larger than in the respective survival models for baseline pain.

Discussion

Our analysis expands the understanding of patient-reported pain in advanced prostate cancer populations into a racially diverse, real-world population assessing multiple dimensions of pain. In a nationwide sample of 879 individuals with newly diagnosed advanced prostate cancer, we found a high prevalence of pain at the time of enrollment, and Black participants experienced more severe pain at study enrollment compared to White participants across multiple scales. We also found that more severe pain on all pain scales at study enrollment and longitudinally was associated with higher mortality independent of clinical factors associated with more aggressive features of advanced prostate cancer. The high prevalence of pain in this study is concerning and reflects an unmet clinical need among this patient population.

Pain is a well-recognized symptom in cancer patients, particularly those living with advanced, metastatic cancer. While Black and White participants had a similar prevalence of high-grade tumors, CRPC, and *de novo* metastatic cancer in our study, PSA levels at enrollment were significantly elevated in Black participants, suggesting a more aggressive cancer. The biologic mechanisms causing pain are complex and poorly understood, involving the interplay between tumor, bone, inflammatory, and nerve cells. Additionally, pain can be caused by the cancer itself or specific cancer therapies and is also influenced by structural racism and individual-level factors.(80–85) Because of this, it is challenging to ascertain the mechanism by which pain is associated with a worse prognosis in our study.

Our finding of racial differences in pain after a new diagnosis of prostate cancer is important in light of the well-known racial disparities in prostate cancer survivorship and mortality. We also found that, in addition to bone pain which is typically investigated in this population, increased pain interference, average pain, and worst pain were all associated with higher mortality after controlling for indicators of disease severity. It will be important for future studies to investigate the different dimensions and facets of pain in this population such as how patients experience the different dimensions of pain, racial bias in provider acknowledgment of pain and analgesic prescribing patterns, and access to therapies to determine the factors upon which to intervene to improve survivorship, particularly for Black individuals.

There are several potential limitations of this analysis. First, this analysis focuses specifically on participants self-identifying as Black or White; it is important to expand this research amongst more racially diverse populations. Second, potential unmeasured confounding by prostate cancer therapy could bias our results because lines of therapy in IRONMAN are currently in the process of being extracted. While ADT and ARSIs (the most commonly received therapies in this population) can alleviate pain due to cancer in untreated disease, they have also been associated with exacerbation of osteoarthritic and back pain,(86,87) leading to a downward bias in our HRs. Third, we did not have access to information on prescription and use of analgesics in the IRONMAN population, which is important given racial differences in prescriptions of analgesics in cancer patients.(65)

Our analysis deepens the understanding of racial disparities in pain and survival in individuals with advanced prostate cancer. Black participants experienced substantially higher pain at study enrollment compared to White participants, and more pain is associated with higher mortality independent of covariates related to disease burden. Our analysis highlights the need for further investigation of the experience and management of pain in this population to improve survivorship, particularly for Black individuals experiencing the most severe pain and highest prostate cancer mortality.

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Appendix 1: Supplementary Material for Chapter 1

Supplementary Table 1.1. Absolute prevalence and prevalence differences (in %) for answering yes to each patient experience measure comparing Black participants to White participants in the IRONMAN cohort, stratified by health center type

	NCI-Designated Centers			***Non-NCI Designated Centers***		
Question	White prevalence (N = 428)	Black prevalence (N = 106)	PD (95% CI)	White prevalence (N = 136)	Black prevalence (N = 31)	PD (95% CI)
Question 1	272 (64%)	73 (70%)	7 (-5, 18)	55 (40%)	22 (73%)	33 (17, 48)
Question 2	232 (55%)	62 (61%)	5 (-6, 18)	60 (44%)	22 (71%)	28 (10, 47)
Question 3	406 (95%)	99 (96%)	0.8 (-4, 5)	121 (90%)	30 (97%)	6 (-1, 16)
Question 4	414 (97%)	102 (99%)	1 (-1, 4)	119 (89%)	30 (97%)	8 (-2, 16)
Question 5	415 (98%)	97 (93%)	-5 (-10, 1)	122 (90%)	30 (97%)	6 (0, 15)
Question 6	375 (88%)	89 (86%)	-1 (-10, 6)	108 (81%)	29 (94%)	13 (3, 25)

All unadjusted models with only race as a covariate. Questions have 0-2 missing responses each; percentage is representative of the proportion of yes answers of all completed responses.

Supplementary Table 1.2: Confirmatory factor analysis (CFA) model fit statistics

*Table S2a: three-factor solution**

	Overall cohort (N=672)	**White participants (N=546)**	**Black participants (N=126)**
Comparative fit index (CFI)	0.989	0.992	0.982
Tucker-Lewis index (TLI)	0.973	0.981	0.954
Root mean square error of approximation (RMSEA)	0.045	0.039	0.045
Standardized root mean square residual (SRMR)	0.058	0.056	0.118

*Table S2b: two-factor solution***

	Overall cohort (N=672)	**White participants (N=546)**	**Black participants (N=126)**
Comparative fit index (CFI)	0.966	0.975	0.942
Tucker-Lewis index (TLI)	0.937	0.954	0.892
Root mean square error of approximation (RMSEA)	0.069	0.061	0.069
Standardized root mean square residual (SRMR)	0.090	0.084	0.148

* Three-factor solution includes: patient information and communication regarding treatment (questions 1 and 2), patient coordination and integration of care (questions 3 and 4), and respect for patient preference (questions 5 and 6)

** Two-factor solution includes: provision of information and services (questions 1, 2, and 6) and communication and patient involvement (questions 3, 4, and 5)

Supplementary Methods

This section describes 1) further reasoning behind our decision regarding what variables to adjust for, 2) more specifics about the marginal standardization procedure that we conducted, and 3) details for the confirmatory factor analysis.

Adjustment variables:

In our study, we considered participants' self-reported race as our "exposure." This is permissible when the research is descriptive or when the effect of race is external to the study participant.(1) As race is a social construct shaped by history and power dynamics, it is not permissible to use race as the primary variable of interest when the effect of race is internal to the participant or to study effect composition to separate biological and social effects of race. Any differences that we expected to see in this study were due to external racism at the individual and systems levels.

The major distinction to make when determining which variables to control for in a regression analysis with race as the exposure is whether you are interested in the total effect of race or specific mediated effects of race. Adjusting for mediating variables (often including socioeconomic status, education, employment, etc) leads to attenuation of the effect of race and should only be used when assessing the remaining disparity due to racism present after accounting for the mediating variables.(2,3) When adjusting for time-invariant variables (e.g. age, sex, etc), the interpretation of the race coefficient in the regression model is the total effect of race on the outcome.(1) Other papers have described the interpretation of the race coefficient when early-life socioeconomic status and later-life socioeconomic status/mediating variables are included in the model for those opting for this interpretation in their analyses.

As patient experience has only been minimally studied in patients with prostate cancer, we chose to investigate the total effect of race to provide a foundation for further investigation

into potential mediating variables and points of intervention. As such, we controlled for the time-invariant variables of age at enrollment and disease state at enrollment.(2,4)

Marginal standardization procedure:

To obtain adjusted prevalence differences, we fit multilevel logistic mixed effects regression models and standardized over the self-reported race variable.(5) To do this, we fit the multilevel logistic mixed effects regression model and cloned our data twice rather than predicting on the observed data.(6) The first clone had all participants set to self-reported race as Black, and the second clone had all participants set to self-reported race as White. We predicted response values for the outcome for each participant under each race level using the cloned datasets and the fitted regression for the initial dataset. We calculated the prevalence difference by averaging the predicted values in the White cloned population and subtracting that from the averaged predicted values in the Black cloned population. Though this prevalence difference is estimated as the difference in prevalence under the two purely hypothetical scenarios where everyone self-reported as Black and everyone self-reported as White, we are not making any causal claims about the prevalence difference and are only using standardization as a means to estimate adjusted prevalence differences.

Confirmatory factor analysis:

Confirmatory factor analysis (CFA) was conducted for the three-factor solution in the overall population as well as stratified by self-reported race. The three latent variables tested were the three defined by Cancer Australia: patient information and communication regarding treatment (questions 1 and 2), patient coordination and integration of care (questions 3 and 4), and respect for patient preference (questions 5 and 6). CFA was estimated using diagonal weighted least square mean and variance adjusted (WLSMV estimators) with robust standard errors, and model fit was assessed using the comparative fit index (CFI, >0.95 indicative of a

good fit), the Tucker-Lewis index (TLI, >0.95 indicative of a good fit), root mean square error of approximation (RMSEA, <0.08 indicative of a good fit), and standardized root mean square residual (SRMR, <0.08 indicative of a good fit). As a previous study (of the full eight-question instrument) found a two-factor solution to be acceptable ("provision of information and services" with questions 1, 2, and 6 and "communication and patient involvement" with questions 3, 4, and 5),(7) this two-factor solution was also tested.

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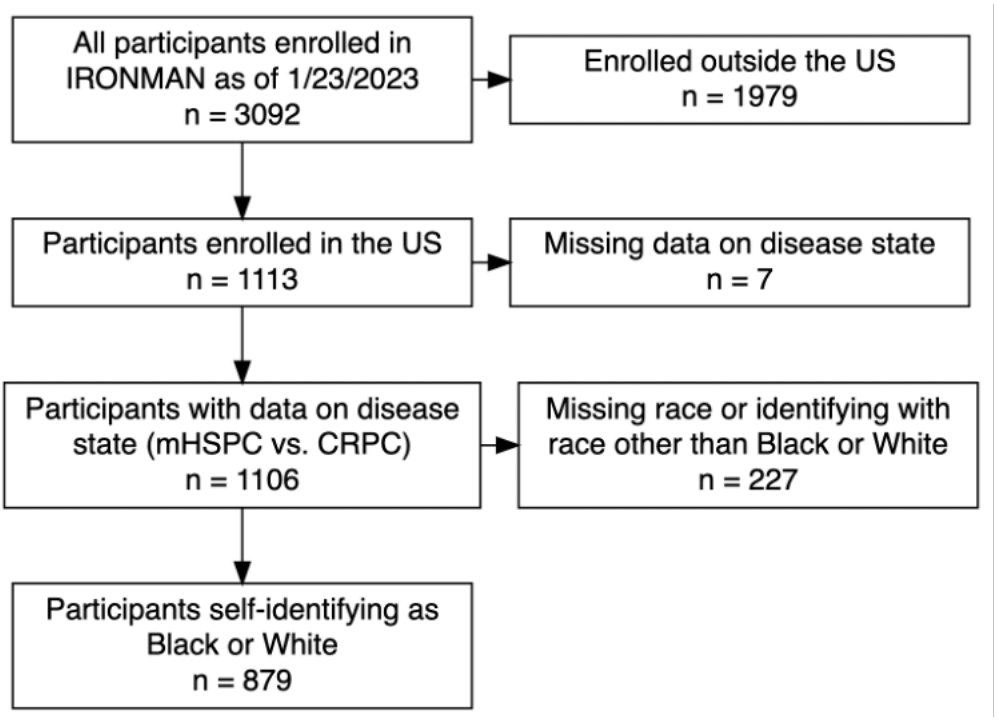
Appendix 2: Supplementary Material for Chapter 2

Supplementary Figure 2.1. Selection of study participants for analysis of quality-of-life data



Supplementary Table 2.1. Study sites for IRONMAN participants in quality-of-life analysis by race (N = 38 sites)

	White (N=704)	Black (N=175)
Baylor College of Medicine	6 (0.9%)	10 (5.7%)
Chesapeake Urology Associates	6 (0.9%)	5 (2.9%)
Columbia University	4 (0.6%)	2 (1.1%)
Dana-Farber Cancer Institute	41 (5.8%)	3 (1.7%)
Delnor Cancer Center	20 (2.8%)	1 (0.6%)
Doylestown Health	14 (2.0%)	0 (0%)
Duke Cancer Network	5 (0.7%)	6 (3.4%)
Duke Comprehensive Cancer Center	55 (7.8%)	11 (6.3%)
Durham VA Medical Center	0 (0%)	5 (2.9%)
Fox Chase Cancer Center - Temple Health	0 (0%)	1 (0.6%)
Kishwaukee Cancer Center	1 (0.1%)	0 (0%)
Memorial Sloan Kettering Cancer Center	65 (9.2%)	8 (4.6%)
Memphis VA Medical Center	4 (0.6%)	6 (3.4%)
Moffitt Cancer Center	3 (0.4%)	0 (0%)
New York-Presbyterian Brooklyn Methodist Hospital	0 (0%)	2 (1.1%)
Oregon Health and Sciences Cancer Center	24 (3.4%)	0 (0%)
Ralph H. Johnson VA Medical Center	10 (1.4%)	5 (2.9%)
Reading Health System	9 (1.3%)	2 (1.1%)
Robert H. Lurie Comprehensive Cancer Center Northwestern University	6 (0.9%)	0 (0%)
Roswell Park Cancer Institute	5 (0.7%)	1 (0.6%)
Sidney Kimmel Comprehensive Cancer Center	7 (1.0%)	6 (3.4%)
Thomas Jefferson University	3 (0.4%)	1 (0.6%)
Tulane University	53 (7.5%)	8 (4.6%)
University of Alabama-Birmingham	4 (0.6%)	3 (1.7%)
University of California Los Angeles	7 (1.0%)	0 (0%)
University of California San Diego	31 (4.4%)	2 (1.1%)
University of Chicago	20 (2.8%)	12 (6.9%)
University of Illinois at Chicago	4 (0.6%)	1 (0.6%)
University of Michigan	27 (3.8%)	4 (2.3%)
University of Mississippi Medical Center	3 (0.4%)	5 (2.9%)

Supplementary Table 2.1 (continued)

	White (N=704)	Black (N=175)
University of North Carolina	31 (4.4%)	8 (4.6%)
University of Virginia	113 (16.1%)	15 (8.6%)
University of Washington	39 (5.5%)	1 (0.6%)
University of Wisconsin	8 (1.1%)	0 (0%)
Warrenville Cancer Center	1 (0.1%)	0 (0%)
Wayne St. University Karmanos Cancer Institute	24 (3.4%)	28 (16.0%)
Weill Cornell Medical Center	44 (6.3%)	4 (2.3%)
Winship Cancer Institute Emory University	7 (1.0%)	9 (5.1%)

Supplementary Table 2.2. Number of participants receiving each therapy category between 3 months before and 12 months after enrollment (N=15 therapy categories)

	Overall (N=879)
ADT	781 (88.9%)
AR Signaling Inhibitor	542 (61.7%)
Chemotherapy	154 (17.5%)
Immunotherapy	48 (5.5%)
Radiopharmaceuticals	21 (2.4%)
PARP	13 (1.5%)
mTOR kinase/DNA-PK Inhibitor	4 (0.5%)
Immunotherapy/Placebo	3 (0.3%)
CDK Inhibitor	2 (0.2%)
Multi-kinase Inhibitor	2 (0.2%)
TGF-ßRI kinase Inhibitor	2 (0.2%)
EZH2 Inhibitor	1 (0.1%)
GR Antagonist	1 (0.1%)
PARP/Placebo	1 (0.1%)
PI3K Inhibitor	1 (0.1%)

Note: participants can fall into more than one group and often are receiving multiple of these therapy categories at the same time)

Supplementary Table 2.3: Longitudinal analysis results for global quality of life score from sensitivity analysis for missing indicator values during MICE procedure (see Supplemental Methods text for more information)

Missing indicator value	Intercept Mean (95% CI)	Race coefficient Mean (95% CI)	Month coefficient Mean (95% CI)	Interaction coefficient Mean (95% CI)	SD of subject random effect	SD of site random effect
-100	70.94 (68.92, 72.95)	-0.72 (-4.19, 2.74)	-0.35 (-0.49, -0.21)	-0.08 (-0.21, 0.06)	15.37	3.28
-150	70.94 (68.93, 72.96)	-0.76 (-4.22, 2.71)	-0.35 (-0.49, -0.21)	-0.08 (-0.21, 0.06)	15.38	3.27
-200	70.94 (68.92, 72.96)	-0.72 (-4.19, 2.75)	-0.35 (-0.49, -0.21)	-0.08 (-0.21, 0.05)	15.38	3.28
-250	70.93 (68.92, 72.95)	-0.70 (-4.17, 2.76)	-0.35 (-0.49, -0.21)	-0.08 (-0.21, 0.06)	15.37	3.29

Supplementary Table 2.4: Longitudinal analysis results from sensitivity analysis excluding individuals who were censored due to being off-study in the first year

	Intercept Mean (95% CI)	Race Coefficient Mean (95% CI)	Month Coefficient Mean (95% CI)	Interaction Coefficient Mean (95% CI)	SD of subject random effect	SD of site random effect
Global Quality of Life (QL)	72.3 (70.5, 74.2)	-1.4 (-4.9, 2.2)	**-0.4 (-0.5, -0.2)**	-0.1 (-0.3, 0)	15.1	2.4
Functioning Scales						
Physical (PF)	85.8 (83.6, 88.1)	**-3.4 (-6.7, 0.2)**	**-0.6 (-0.7, -0.5)**	**-0.4 (-0.5, -0.3)**	14.2	3.8
Emotional (EF)	82.1 (80.2, 84.0)	**4.7 (1.6, 7.8)**	-0.1 (-0.2, 0)	**0.2 (0.1, 0.4)**	13.2	3.2
Social (SF)	81.8 (79.2, 84.3)	0.8 (-3.3, 4.8)	**-0.3 (-0.4, -0.1)**	0 (-0.1, 0.2)	15.8	4.8
Role (RF)	82.5 (79.8, 85.2)	-2.2 (-6.7, 2.3)	**-0.7 (-0.8, -0.5)**	-0.1 (-0.3, 0)	17.6	4.6
Cognitive (CF)	85.0 (83.0, 87.0)	0.1 (-3.1, 3.4)	**-0.3 (-0.5, -0.2)**	0 (-0.2, 0.1)	13.6	3.5
Symptom Scales						
Fatigue (FA)	29.0 (26.4, 31.5)	-1.0 (-5.0, 3.1)	**0.6 (0.4, 0.7)**	0 (-0.1, 0.2)	16.8	4.7
Nausea/vomiting (NV)	3.6 (2.9, 4.3)	**2.2 (0.5, 3.9)**	0 (-0.1, 0.1)	**-0.1 (-0.2, -0.1)**	6.0	0.0
Pain (PA)	17.6 (15.1, 20.1)	4.0 (-0.3, 8.2)	**0.4 (0.2, 0.6)**	**-0.3 (-0.4, -0.1)**	17.6	4.5
Dyspnea (DY)	13.3 (11.0, 15.7)	1.8 (-2.3, 5.9)	**0.5 (0.4, 0.7)**	0.2 (0, 0.4)	17.3	3.5
Sleep (SL)	29.3 (26.6, 32.0)	**-9.0 (-13.8, -4.2)**	0.1 (-0.1, 0.3)	**-0.3 (-0.5, -0.1)**	19.7	4.0
Appetite (AP)	9.4 (7.6, 11.1)	3.4 (-0.1, 6.8)	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	13.2	2.1
Constipation (CO)	11.6 (9.9, 13.3)	**6.9 (3.2, 10.6)**	**0.2 (0.1, 0.4)**	0.2 (0, 0.3)	14.4	0.9
Diarrhea (DI)	10.0 (8.1, 11.8)	-2.0 (-5.1, 1.2)	0.1 (-0.1, 0.2)	-0.1 (-0.2, 0)	11.5	3.1
Financial insecurity (FI)	15.4 (12.8, 18.0)	**5.2 (0.8, 9.7)**	-0.1 (-0.3, 0)	**-0.6 (-0.8, -0.4)**	19.6	4.4

Supplementary Table 2.5: Longitudinal analysis results for study participants with metastatic hormone sensitive prostate cancer (mHSPC) at IRONMAN enrollment (N = 573)

	Intercept Mean (95% CI)[a]	Race coefficient Mean (95% CI)[b]	Month coefficient Mean (95% CI)[b]	Interaction coefficient Mean (95% CI)[b]
Global Quality of Life (QL)	71.1 (68.8, 73.4)	**0.5 (0.3, 0.6)**	**-0.3 (-0.5, -0.2)**	-0.1 (-0.5, 0.3)
Functioning Scales				
Physical (PF)	85.8 (83.5, 88.1)	**-5.0 (-5.1, -4.9)**	**-0.6 (-0.8, -0.5)**	**-0.4 (-0.8, -0.1)**
Emotional (EF)	80.1 (78.0, 82.1)	**5.4 (5.3, 5.6)**	-0.1 (-0.2, 0.1)	0.3 (-0.1, 0.6)
Social (SF)	81.0 (78.2, 83.8)	0.1 (-0.1, 0.3)	**-0.2 (-0.4, -0.1)**	0 (-0.5, 0.5)
Role (RF)	80.2 (77.0, 83.4)	**-2.6 (-2.8, -2.4)**	**-0.6 (-0.8, -0.4)**	-0.1 (-0.6, 0.5)
Cognitive (CF)	84.2 (81.9, 86.4)	**1.0 (0.8, 1.1)**	**-0.4 (-0.5, -0.2)**	0 (-0.4, 0.4)
Symptom Scales				
Fatigue (FA)	29.6 (27.0, 32.2)	**0.3 (0.1, 0.4)**	**0.6 (0.4, 0.8)**	-0.1 (-0.5, 0.4)
Nausea/vomiting (NV)	4.0 (3.1, 5.0)	**2.4 (2.3, 2.5)**	0 (-0.1, 0.1)	-0.2 (-0.4, 0.1)
Pain (PA)	18.6 (15.7, 21.5)	**5.3 (5.1, 5.5)**	**0.4 (0.2, 0.6)**	-0.3 (-0.7, 0.2)
Dyspnea (DY)	14.1 (11.5, 16.7)	**0.7 (0.5, 0.9)**	**0.6 (0.4, 0.8)**	0.1 (-0.3, 0.6)
Sleep (SL)	31.7 (28.6, 34.7)	**-9.3 (-9.5, -9.0)**	0.2 (0, 0.4)	-0.4 (-1.0, 0.2)
Appetite (AP)	10.7 (8.6, 12.7)	**2.5 (2.3, 2.7)**	-0.1 (-0.2, 0.1)	0 (-0.4, 0.5)
Constipation (CO)	12.4 (10.1, 14.7)	**8.9 (8.7, 9.1)**	**0.2 (0.1, 0.4)**	0.2 (-0.3, 0.7)
Diarrhea (DI)	9.7 (8.0, 11.4)	**-3.1 (-3.2, -2.9)**	0 (-0.1, 0.2)	-0.2 (-0.6, 0.2)
Financial insecurity (FI)	17.5 (14.3, 20.4)	**7.1 (7.0, 7.3)**	**-0.3 (-0.5, -0.1)**	-0.6 (-1.1, -0.1)

[a] Crude model adjusted including race only
[b] Adjusted model including race and age at enrollment (continuous) variables

Supplementary Table 2.6: Longitudinal analysis results for study participants with castration resistant prostate cancer (CRPC) at IRONMAN enrollment (N = 306)

	Intercept Mean (95% CI)[a]	Race coefficient Mean (95% CI)[b]	Month coefficient Mean (95% CI)[b]	Interaction coefficient Mean (95% CI)[b]
Global Quality of Life (QL)	71.1 (68.1, 74.2)	**-2.7 (-3.0, -2.5)**	**-0.4 (-0.6, -0.2)**	0 (-0.6, 0.5)
Functioning Scales				
Physical (PF)	82.8 (79.1, 86.5)	**1.4 (1.2, 1.6)**	**-0.5 (-0.7, -0.3)**	-0.4 (-0.8, 0.1)
Emotional (EF)	84.2 (81.7, 86.6)	**4.1 (4.0, 4.3)**	-0.2 (-0.4, 0)	0.3 (-0.1, 0.8)
Social (SF)	81.5 (78.4, 84.7)	**1.7 (1.5, 2.0)**	**-0.3 (-0.6, -0.1)**	0.1 (-0.5, 0.7)
Role (RF)	82.4 (79.0, 85.8)	**1.9 (1.6, 2.2)**	**-0.7 (-1.0, -0.5)**	-0.2 (-0.9, 0.5)
Cognitive (CF)	85.3 (82.9, 87.7)	**-0.7 (-0.9, -0.5)**	**-0.3 (-0.5, -0.1)**	-0.1 (-0.6, 0.3)
Symptom Scales				
Fatigue (FA)	30.2 (26.7, 33.7)	**-4.7 (-4.9, -4.4)**	**0.6 (0.3, 0.9)**	0.1 (-0.5, 0.7)
Nausea/vomiting (NV)	4.3 (2.8, 5.8)	**2.5 (2.3, 2.6)**	0 (-0.1, 0.2)	-0.2 (-0.6, 0.1)
Pain (PA)	18.8 (15.1, 22.5)	**3.5 (3.2, 3.8)**	**0.3 (0.1, 0.6)**	-0.3 (-1.0, 0.4)
Dyspnea (DY)	12.4 (9.7, 15.1)	**2.3 (2.1, 2.6)**	**0.4 (0.2, 0.7)**	0.3 (-0.3, 0.8)
Sleep (SL)	26.6 (23.3, 30.0)	**-5.4 (-5.7, -5.1)**	-0.1 (-0.3, 0.2)	-0.2 (-0.9, 0.5)
Appetite (AP)	10.3 (6.9, 13.8)	**2.6 (2.3, 2.8)**	0.3 (0, 0.5)	-0.1 (-0.7, 0.5)
Constipation (CO)	12.1 (9.4, 14.8)	**2.3 (2.0, 2.5)**	0.2 (0, 0.4)	0 (-0.6, 0.5)
Diarrhea (DI)	11.2 (7.9, 14.5)	**0.9 (0.7, 1.2)**	0.2 (0, 0.4)	0 (-0.6, 0.6)
Financial insecurity (FI)	13.0 (10.0, 16.1)	**3.9 (3.6, 4.1)**	0.2 (-0.1, 0.5)	-0.6 (-1.2, 0)

[a] Crude model adjusted including race only
[b] Adjusted model including race and age at enrollment (continuous) variables

Supplementary Methods

This section describes 1) further reasoning behind our decision regarding what variables to adjust for in the longitudinal analyses, 2) an overview of the missing data methods in our analysis (broken down into missing individual variables on completed questionnaires, missing whole questionnaires while on study, and missing questionnaires due to censoring), and 3) rationale for our chosen longitudinal model.

***Adjustment variables**:*

In our study, we considered participants' self-reported race as our "exposure." This is permissible when the research is descriptive or when the effect of race is external to the study participant.(1) Race is a social construct shaped by history and power dynamics, and it should not be conceptualized as internal to the participant or used in an effort to separate biological and social effects of race. Any differences that we expected to see in this study were due to external racism at the individual and systems levels.

The major distinction to make when determining which variables to control for in a regression analysis with race as the exposure is whether you are interested in the total effect of race or specific mediated effects of race. Adjusting for mediating variables (often including socioeconomic status, education, employment, etc) leads to attenuation of the effect estimate of race and should only be used when assessing the remaining disparity due to racism present after accounting for the mediating variables.(2,3) When adjusting for time-invariant variables (e.g. age, sex, etc), the interpretation of the race coefficient in the regression model is the total effect of race on the outcome.(1) Other papers have described the interpretation of the race coefficient when early-life socioeconomic status and later-life socioeconomic status/mediating variables are included in the model for those opting for this interpretation in their analyses.(2)

As quality of life has only been minimally studied in a racially diverse group of patients with prostate cancer, we chose to investigate the total effect of race to provide a foundation for further investigation into potential mediating variables and points of intervention. As such, we controlled for the time-invariant variables of age at enrollment and disease state at enrollment, both shaped by racism and when a patient presents for care and is diagnosed.(2,4)

Missing data methods:

Missing individual variables on completed questionnaires

We began by exploring missing data on questionnaires that were completed by the participants. The completion of each of the 30 individual EORTC outcome questions on 3089 completed questionaires are shown in **Supplementary Table SM2.1** and **Supplementary Table SM2.2** below.

Supplementary Table SM2.1: Missingness of individual outcome questions on 3089 completed questionnaires

Question (number missing)	Q1 (27)	Q2 (27)	Q3 (35)	Q4 (28)	Q5 (22)	Q6 (29)	Q7 (33)	Q8 (29)	Q9 (28)	Q10 (39)	Q11 (30)	Q12 (27)	Q13 (28)	Q14 (35)	Q15 (24)
	Q16 (31)	Q17 (33)	Q18 (39)	Q19 (38)	Q20 (32)	Q21 (35)	Q22 (30)	Q23 (27)	Q24 (36)	Q25 (35)	Q26 (30)	Q27 (34)	Q28 (44)	Q29 (40)	Q30 (34)

Supplementary Table SM2.2: Total outcome questions missing on completed questionnaires

Number of questions missing	0	1	2	3	4	5	6	7	9	11	12	14	15	30
Number of questionnaires with missing questions	2850	134	41	16	6	6	5	6	2	1	2	2	2	15

Over 92% of the completed questionnaires were fully completed in regard to the 30 individual EORTC outcome variables. Questionnaires that were completed but missing more than 10 of 30 individual EORTC questions were marked as fully missing for purposes of the analysis.

We used multiple imputation by chained equations (MICE) to create imputed datasets for the missing outcomes. As we were interested in the scale scores for the EORTC questionnaire as our outcome, we calculated the EORTC scale scores where all items part of the scale were complete and imputed the scale scores.(5) We began by making a long dataset where each row represented a single timepoint for one individual. As we only wanted to impute the missing outcomes on completed questionnaires, we set the outcome scales on missing full questionnaires to a value of -250 to serve as a missing indicator during the imputation (needing the value to be numeric and also not wanting the number to be within the 0 to 100 range of the outcome scales which could bias the results). We then converted to a wide dataset with one row per individual to preserve clustering by participant during the imputation process.

MICE was conducted on the wide dataset using the following variables: participant ID, race, marital status, highest education attained, employment status, military status, study site ID, metastatic status at baseline, disease state at enrollment, age, PSA, Gleason score, whether or not they were censored during the first year, and whether or not they completed all possible on-study questionnaires. We used the MICE method of classification and regression trees and constrained the outcome variable imputations to be between 0 and 100 (inclusive of the bounds) in alignment with the possible range of the EORTC scales. We created 10 imputed datasets using 10 iterations for each imputation to stabilize. After the MICE procedure, we had full outcome scale data for completed questionnaires and full covariate data for all participants. We then converted back to a long dataset and returned the indicator values of -250 back to missing.

We conducted a sensitivity analysis using different values for the missing indicator to determine how robust our results of the longitudinal analysis were to the chosen value. We chose to test missing indicator values of -200, -150, and -100 for our sensitivity analysis; the results of this sensitivity analysis for the crude longitudinal analysis of the overall quality of life scale are shown in **Supplementary Table 2.3.** Similarly small differences between the results

for the various missing indicator values were observed for other scales as well (data not shown). The value of -250 was chosen for the final analysis as it was the furthest from the 0-100 scale of the EORTC outcomes.

Supplementary Table 2.3 (repeated from above): Longitudinal analysis results for global quality of life score from sensitivity analysis for missing indicator values during MICE procedure

Missing indicator value	Intercept Mean (95% CI)	Race coefficient Mean (95% CI)	Month coefficient Mean (95% CI)	Interaction coefficient Mean (95% CI)	SD of subject random effect	SD of site random effect
-100	70.94 (68.92, 72.95)	-0.72 (-4.19, 2.74)	-0.35 (-0.49, -0.21)	-0.08 (-0.21, 0.06)	15.37	3.28
-150	70.94 (68.93, 72.96)	-0.76 (-4.22, 2.71)	-0.35 (-0.49, -0.21)	-0.08 (-0.21, 0.06)	15.38	3.27
-200	70.94 (68.92, 72.96)	-0.72 (-4.19, 2.75)	-0.35 (-0.49, -0.21)	-0.08 (-0.21, 0.05)	15.38	3.28
-250	70.93 (68.92, 72.95)	-0.70 (-4.17, 2.76)	-0.35 (-0.49, -0.21)	-0.08 (-0.21, 0.06)	15.37	3.29

Missing full questionnaires while on study

To understand the missingness of whole questionnaires, we began by determining the proportion of on-study individuals completing the questionnaire at each timepoint (**Supplementary Table SM2.3**) and the proportion of individuals completing each level of 0 to 5 questionnaires during the first year of follow-up (**Supplementary Table SM2.4**).

Supplementary Table SM2.3: Proportion of questionnaires completed by on-study participants

Timepoint	Number of on-study participants with timepoint passed	Completed questionnaires (N, %)
0	879	765 (87.0)
3	847	673 (79.5)
6	779	595 (76.4)
9	733	552 (75.3)
12	678	504 (74.3)

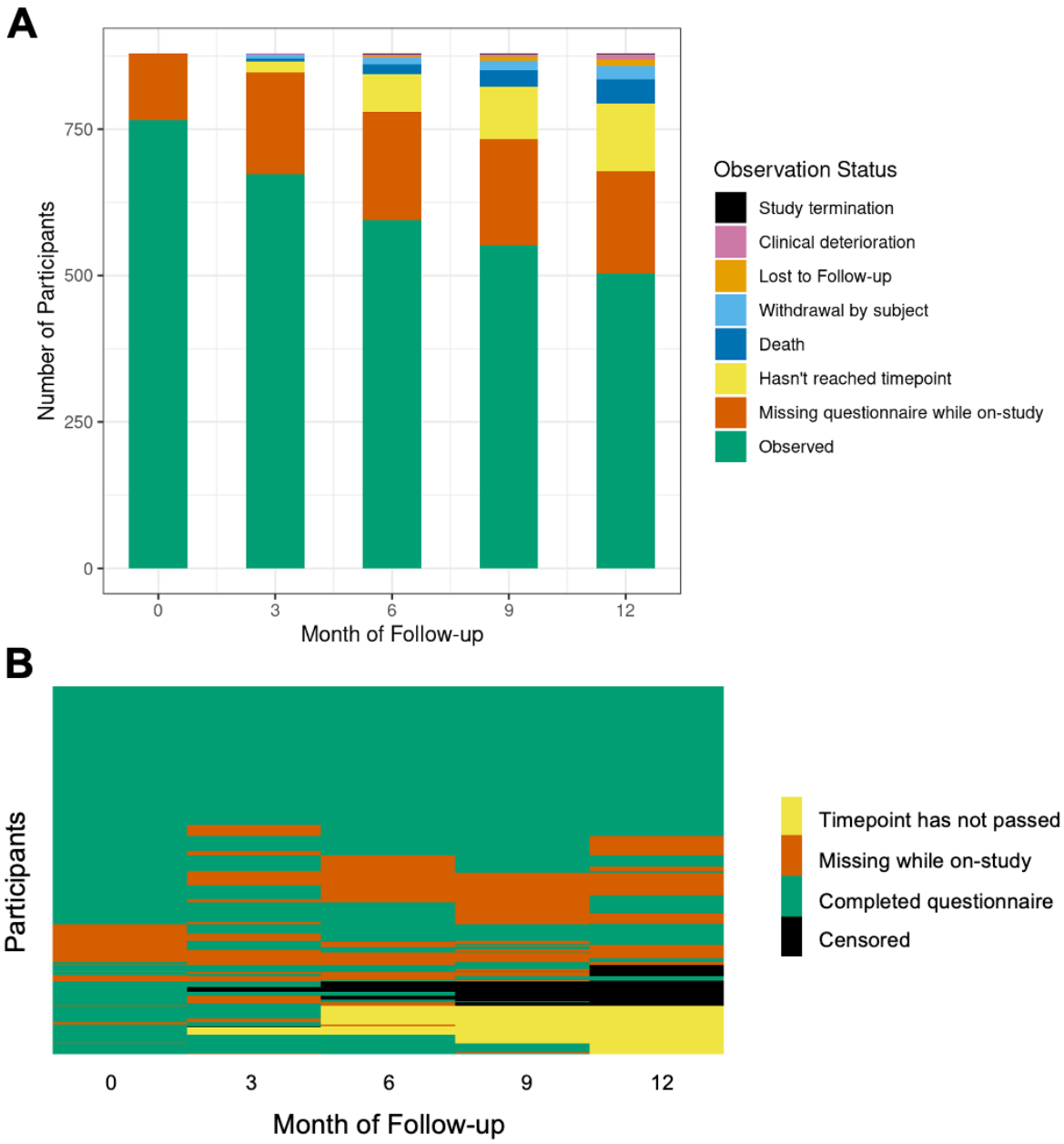
Supplementary Table SM2.4: Proportion of 879 participants completing given number of questionnaires

Number of questionnaires	Participants completing number of questionnaires in first year, N (%)
0	11 (1.3)
1	118 (13.4)
2	122 (13.9)
3	127 (14.4)
4	159 (18.1)
5	342 (38.9)

There was generally high completion of questionnaires in this cohort over the first year. When individuals were on-study, a majority of individuals did complete the questionnaire, even at one year after enrollment (74.3%). Approximately 40% of participants completed all five questionnaires in the first year; others missed questionnaires either due to censoring, the timepoint not passing yet, or being on-study but missing the questionnaire.

To visualize the longitudinal missingness in the data, we created **Figure 2.1** in the main paper, copied again here. **Figure 2.1A** shows the proportion of participants with each type of observation status for the questionnaire at the given timepoints. **Figure 2.1B** shows the longitudinal missing data patterns for each individual according to four categories: 1) completed questionnaire, 2) missing questionnaire while on-study, 3) timepoint not yet passed, and 4) censored.

Figure 2.1A: Proportion of the observation status for whole questionnaires at each timepoint
Figure 2.1B: Longitudinal missing data patterns for whole questionnaires for each participant



We saw that the majority of participants who have the opportunity to complete each questionnaire do so. We also saw that the longitudinal missingness in whole questionnaires was clearly non-monotone: many participants would miss a questionnaire while on-study and complete a questionnaire at a later timepoint. Thirty missing data patterns are present in the longitudinal data.

To determine if there were differences in the demographics of participants who completed all possible questionnaires compared to those who did not complete at least one questionnaire while on-study, we compared covariate distributions from one of the imputed datasets for these two groups (shown in **Supplementary Table SM2.5**). No major differences in any of the covariates were noted between those who completed all questionnaires and those who missed at least one while on-study.

Supplementary Table SM2.5: Covariate distributions stratified by questionnaire completeness

	Complete (N=464)	Incomplete (N=415)	P-value
Age at study entry, years			
Mean (SD)	69.27 (8.67)	68.79 (9.24)	0.428
Self-identified race			
White	382 (82%)	322 (78%)	0.0947
Black	82 (18%)	93 (22%)	
Disease state at enrollment			
CRPC	159 (34%)	147 (35%)	0.774
mHSPC	305 (66%)	268 (65%)	
Highest education level at baseline			
Less than College	95 (20%)	94 (23%)	0.809
Some College or Bachelor's Degree	141 (30%)	128 (31%)	
Vocational School/Program	8 (2%)	4 (1%)	
Graduate Degree	210 (45%)	180 (43%)	
Other	10 (2%)	9 (2%)	
Marital status at baseline			
Married	343 (74%)	297 (72%)	0.765
In a Civil Partnership	10 (2%)	12 (3%)	
Widowed	22 (5%)	19 (5%)	
Divorced/Separated	64 (14%)	57 (14%)	
Never Married	25 (5%)	30 (7%)	
Employment status at baseline			
Retired	274 (59%)	220 (53%)	0.268
Working Full-Time	119 (26%)	129 (31%)	

	Complete (N=464)	Incomplete (N=415)	P-value
Working Part-Time	36 (8%)	33 (8%)	
Unemployed	12 (3%)	16 (4%)	
Disabled	23 (5%)	17 (4%)	
Member of national military at baseline			
Yes, currently or previously	144 (31%)	140 (34%)	0.434
No, I have never served in the national military	320 (69%)	275 (66%)	
Prostatectomy or biopsy gleason score			
6 or less	20 (4%)	16 (4%)	0.953
7	135 (29%)	123 (30%)	
8	80 (17%)	76 (18%)	
9-10	229 (49%)	200 (48%)	
First on-study PSA (ng/mL)			
Mean (SD)	71.78 (359.12)	130.77 (548.14)	0.0628
Censoring status			
Censored	45 (10%)	43 (10%)	0.83
Not Censored	419 (90%)	372 (90%)	

We then wanted to assess whether or not global self-reported quality of life at a given timepoint predicted whether or not the participant returned for the questionnaire at the following timepoint. For each of the four intervals (month 0 to month 3, month 3 to month 6, month 6 to month 9, and month 9 to month 12), we subset a fully-imputed dataset to include only those who had completed the questionnaire at the earlier timepoint. We then further subset the data to only include individuals who either completed the questionnaire at the later timepoint or were on study but did not fill out the questionnaire at the later timepoint. We did not include individuals who were censored or for whom the later timepoint had not yet passed as we were specifically interested in assessing the non-monotone missingness of on-study questionnaires in this analysis. For each of the four intervals, we ran a logistic regression model with the global quality of life scale at the earlier timepoint as the only predictor and assessed the significance of the coefficient to determine the extent to which global quality of life predicted completion of the

questionnaire at the following timepoint (outcome 1 = completed following questionnaire; 2 = did not complete following questionnaire). The results for this analysis are shown in **Supplementary Table SM2.6**. Other scale scores showed similar results (data not shown).

Supplementary Table SM2.6: Global QL scale as a predictor of completion of questionnaire at following timepoint

	Month 0 to Month 3	Month 3 to Month 6	Month 6 to Month 9	Month 9 to Month 12
Global QL scale score				
Mean (SE)	0.005 (0.005)	0.011 (0.005)	0.019 (0.006)	0.009 (0.006)
P-value	0.28	0.03	0.001	0.12

From this analysis, we saw that a higher global quality of life at month 3 was predictive of completing the questionnaire at month 6, and the same for month 6 to month 9. These results were not consistent, however, for the month 0 to month 3 interval or the month 9 to month 12 interval. We did not find strong evidence for a consistent association of quality of life domains predicting whether or not an individual returned for a later questionnaire.

Similarly, we wanted to assess whether various demographic and clinical covariate distributions were different for individuals who did not complete a questionnaire and then completed a questionnaire at the following timepoint. As these individuals did not complete the earlier questionnaire, we could not use outcome scores as predictors and instead had to assess covariate distributions. We assessed the same four time intervals as previously described. For each of the four time intervals, we subset a fully-imputed dataset to include only individuals who did not complete the questionnaire at the earlier timepoint, and either completed the questionnaire or continued to have a missing questionnaire while on study at the following timepoint. The results for this analysis are shown in **Supplementary Table SM2.7A and SM2.7B.**

Supplementary Table SM2.7A: Covariate distributions for those entering or remaining missing from month 0 to month 6

	Month 0 to Month 3			Month 3 to Month 6		
	Enter (N=60)	**Missing (N=59)**	**P-value**	**Enter (N=73)**	**Missing (N=88)**	**P-value**
Self-identified race						
White	48 (80.0%)	49 (83.1%)	0.847	59 (80.8%)	66 (75.0%)	0.489
Black	12 (20.0%)	10 (16.9%)		14 (19.2%)	22 (25.0%)	
Disease state at enrollment						
CRPC	19 (31.7%)	16 (27.1%)	0.731	22 (30.1%)	33 (37.5%)	0.416
mHSPC	41 (68.3%)	43 (72.9%)		51 (69.9%)	55 (62.5%)	
Age at study entry, years						
Mean (SD)	67.43 (8.03)	67.86 (9.52)	0.790	67.74 (9.15)	69.06 (9.11)	0.364
Marital status at baseline						
Married	46 (76.7%)	46 (78.0%)	0.945	54 (74.0%)	67 (76.1%)	0.883
In a Civil Partnership	2 (3.3%)	1 (1.7%)		2 (2.7%)	1 (1.1%)	
Widowed	2 (3.3%)	1 (1.7%)		3 (4.1%)	5 (5.7%)	
Divorced/Separated	5 (8.3%)	5 (8.5%)		7 (9.6%)	9 (10.2%)	
Never Married	5 (8.3%)	6 (10.2%)		7 (9.6%)	6 (6.8%)	
Highest education level at baseline						
Less than College	6 (10.0%)	10 (16.9%)	0.667	19 (26.0%)	17 (19.3%)	0.268
Some College or Bachelor's Degree	24 (40.0%)	22 (37.3%)		20 (27.4%)	33 (37.5%)	
Vocational School/Program	1 (1.7%)	1 (1.7%)		2 (2.7%)	0 (0%)	
Graduate Degree	29 (48.3%)	25 (42.4%)		31 (42.5%)	35 (39.8%)	
Other	0 (0%)	0 (0%)		1 (1.4%)	3 (3.4%)	
Employment status at baseline						
Retired	27 (45.0%)	32 (54.2%)	0.616	38 (52.1%)	48 (54.5%)	0.443
Working Full-Time	22 (36.7%)	20 (33.9%)		22 (30.1%)	29 (33.0%)	
Working Part-Time	7 (11.7%)	4 (6.8%)		5 (6.8%)	8 (9.1%)	
Unemployed	1 (1.7%)	2 (3.4%)		5 (6.8%)	2 (2.3%)	
Disabled	3 (5.0%)	1 (1.7%)		3 (4.1%)	1 (1.2%)	
Member of national military at baseline						
Yes, currently or previously	20 (33.3%)	15 (25.4%)	0.456	20 (27.4%)	36 (40.9%)	0.104
No, I have never served in the national military	40 (66.7%)	44 (74.6%)		53 (72.6%)	52 (59.1%)	

	Month 0 to Month 3			Month 3 to Month 6		
	Enter (N=60)	**Missing (N=59)**	**P-value**	**Enter (N=73)**	**Missing (N=88)**	**P-value**
First on-study PSA (ng/mL)						
Mean (SD)	129.85 (478.57)	175.13 (818.97)	0.714	115.57 (428.10)	141.01 (691.34)	0.742
Prostatectomy or biopsy gleason score						
6 or less	1 (1.7%)	3 (5.1%)	0.373	1 (1.4%)	4 (4.5%)	0.702
7	20 (33.3%)	14 (23.7%)		21 (28.8%)	25 (28.4%)	
8	10 (16.7%)	15 (25.4%)		15 (20.5%)	16 (18.2%)	
9-10	29 (48.3%)	27 (45.8%)		36 (49.3%)	43 (48.9%)	

Supplementary Table SM2.7B: Covariate distributions for those entering or remaining missing from month 6 to month 12

	Month 6 to Month 9			Month 9 to Month 12		
	Enter (N=64)	Missing (N=111)	P-value	Enter (N=62)	Missing (N=103)	P-value
Self-identified race						
White	55 (85.9%)	75 (67.6%)	0.0125	48 (77.4%)	73 (70.9%)	0.460
Black	9 (14.1%)	36 (32.4%)		14 (22.6%)	30 (29.1%)	
Disease state at enrollment						
CRPC	22 (34.4%)	44 (39.6%)	0.596	24 (38.7%)	35 (34.0%)	0.655
mHSPC	42 (65.6%)	67 (60.4%)		38 (61.3%)	68 (66.0%)	
Age at study entry, years						
Mean (SD)	68.06 (8.08)	69.02 (9.12)	0.474	67.66 (9.50)	69.04 (8.53)	0.351
Marital status at baseline						
Married	42 (65.6%)	81 (73.0%)	0.319	45 (72.6%)	76 (73.8%)	0.990
In a Civil Partnership	2 (3.1%)	3 (2.7%)		2 (3.2%)	4 (3.9%)	
Widowed	1 (1.6%)	6 (5.4%)		2 (3.2%)	4 (3.9%)	
Divorced/Separated	15 (23.4%)	14 (12.6%)		89 (14.5%)	14 (13.6%)	
Never Married	4 (6.3%)	7 (6.3%)		4 (6.5%)	5 (4.9%)	
Highest education level at baseline						
Less than College	11 (17.2%)	24 (21.6%)	0.711	12 (19.4%)	29 (28.2%)	0.0106
Some College or Bachelor's Degree	26 (40.6%)	35 (31.5%)		29 (46.8%)	21 (20.4%)	
Vocational School/Program	0 (0%)	1 (0.9%)		0 (0%)	1 (1.0%)	
Graduate Degree	25 (39.1%)	48 (43.2%)		20 (32.3%)	49 (47.6%)	
Other	2 (3.1%)	3 (2.7%)		1 (1.6%)	3 (2.9%)	
Employment status at baseline						
Retired	30 (46.9%)	62 (55.9%)	0.532	32 (51.6%)	54 (52.4%)	0.397
Working Full-Time	23 (35.9%)	36 (32.4%)		22 (35.5%)	36 (35.0%)	
Working Part-Time	5 (7.8%)	8 (7.2%)		4 (6.5%)	8 (7.8%)	
Unemployed	4 (6.3%)	2 (1.8%)		0 (0%)	3 (2.9%)	
Disabled	2 (3.1%)	3 (2.7%)		4 (6.5%)	2 (1.9%)	
Member of national military at baseline						
Yes, currently or previously	15 (23.4%)	44 (39.6%)	0.0436	27 (43.5%)	35 (34.0%)	0.288
No, I have never served in the national military	49 (76.6%)	67 (60.4%)		35 (56.5%)	68 (66.0%)	

	Month 6 to Month 9			Month 9 to Month 12		
	Enter (N=64)	**Missing (N=111)**	**P-value**	**Enter (N=62)**	**Missing (N=103)**	**P-value**
First on-study PSA (ng/mL)						
Mean (SD)	65.72 (154.31)	163.81 (706.69)	0.162	86.44 (384.60)	212.24 (882.64)	0.209
Prostatectomy or biopsy gleason score						
6 or less	3 (4.7%)	5 (4.5%)	0.54	1 (1.6%)	6 (5.8%)	0.327
7	22 (34.4%)	38 (34.2%)		19 (30.6%)	35 (34.0%)	
8	8 (12.5%)	24 (21.6%)		16 (25.8%)	17 (16.5%)	
9-10	31 (48.4%)	44 (39.6%)		26 (41.9%)	45 (43.7%)	

From this analysis, we also did not see any strong evidence for consistent trends across time intervals regarding covariate distributions differing between those who completed a questionnaire after missing one and those who missed two questionnaires in a row while on-study. **Overall, these assessments of missing whole questionnaires while on-study did not identify variables that were consistently and strongly associated with the non-monotone missingness of questionnaires.**

Missing questionnaires due to censoring

After evaluating the non-monotone missingness of the data, we assessed the missingness of whole questionnaires due to the individual being censored (in this context, specifically individuals who were censored due to being off-study at any point in the first year; this does not include individuals who haven't accrued enough person-time to complete a given questionnaire). Reasons for being off-study in the first year by race is shown in **Supplementary Table SM2.8.**

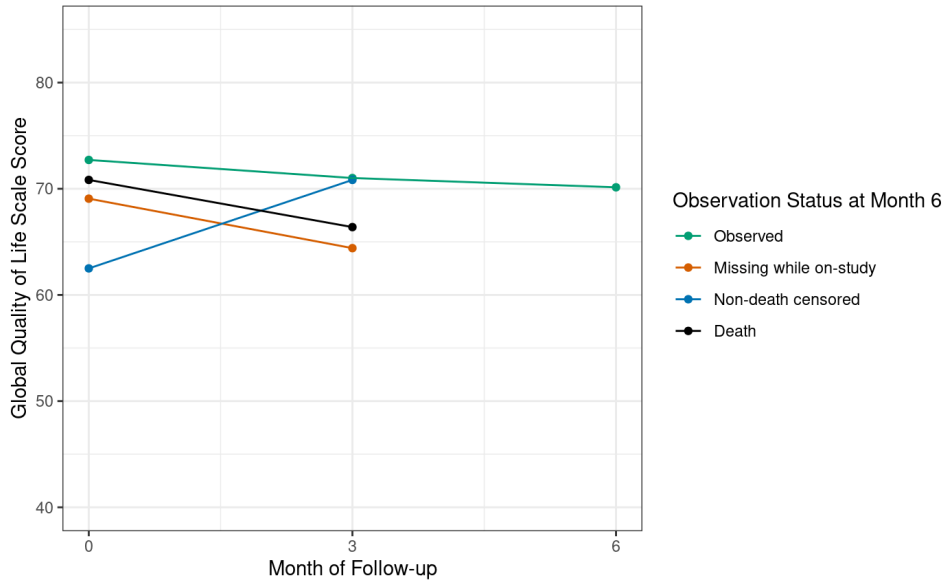
Supplementary Table SM2.8: Off-study reasons by race

Reason for being off-study	White participants			Black participants		
	Number of participants	Proportion of those censored (N = 64)	Proportion of those enrolled (N = 704)	Number of participants	Proportion of those censored (N = 25)	Proportion of those enrolled (N = 175)
Death	32	50.0%	4.5%	12	48.0%	6.9%
Withdrawal by participant	18	28.1%	2.6%	5	20.0%	2.9%
Lost to follow-up	9	14.1%	1.3%	4	16.0%	2.3%
Clinical deterioration	4	6.3%	0.6%	4	16.0%	2.3%
Study termination	1	1.6%	0.1%	0	0%	0%

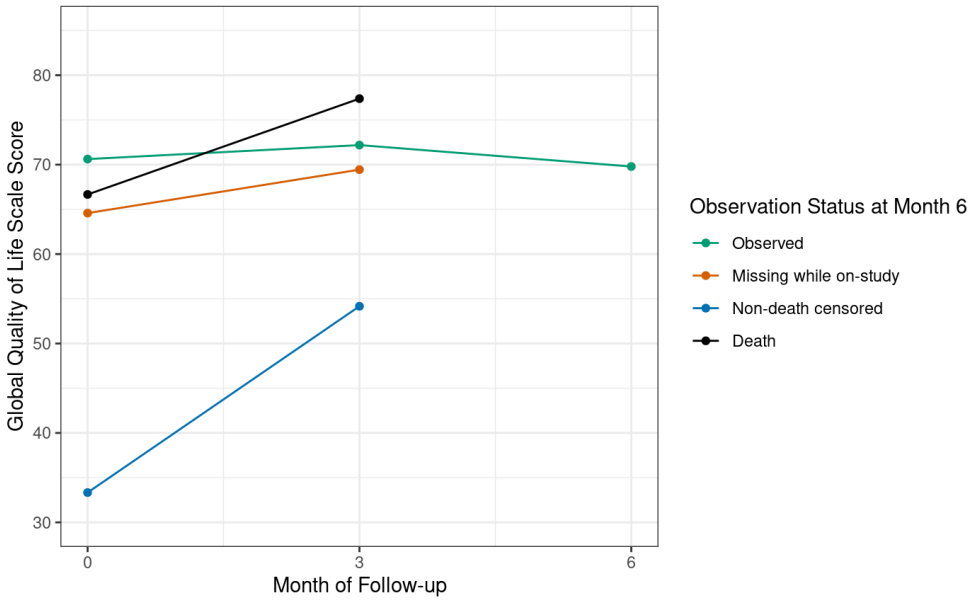
A small proportion of participants are censored over the first year of follow-up. Approximately 90% of participants remain on-study over the first year. The most common reason for censoring was death, representing approximately 50% of the reasons for being off-study in the first year but only 4.5% of the total White population and 6.9% of the total Black population.

We conducted a trajectory analysis to assess whether the trajectory for global quality of life between month 0 and month 3 was predictive of observation status of the questionnaire at month 6 (completed questionnaire, missing questionnaire while on-study, censoring due to death, and censoring due to reasons other than death). We expected that quality of life would decrease for the latter three groups between month 0 and month 3, leading the individual to not complete the month 6 questionnaire. We subset a fully-imputed dataset to include only individuals who completed both the month 0 and month 3 questionnaires and plotted the trajectories stratified by race. These results are shown in **Supplementary Figure SM2.1A and SM2.1B** below.

Supplementary Figure SM2.1A: trajectory analysis for White participants between month 0 and month 6



Supplementary Figure SM1b: trajectory analysis for Black participants between month 0 and month 6



For both White and Black participants, individuals who were censored for reasons other than death at month 6 had a sharp increase in global quality of life between month 0 and month

3. For those who were censored due to death, quality of life decreases in the months prior to death for White participants, whereas quality of life increases in the months prior to death for Black participants. Opposing results were also shown for those who were missing the month 6 questionnaire while still on-study: White participants had a decrease in global quality of life leading up to month 6 whereas Black participants had an increase. As these results are inconsistent by race and often the opposite of what we hypothesized, we do not see strong patterns in quality of life trajectories prior to missing a questionnaire (due to either censoring or other reasons).

Finally, we wanted to assess whether those who were censored during the first year of follow-up had different covariate distributions compared to those who remained on-study for the first year. The results for this analysis are shown in **Supplementary Table SM2.9** below.

Supplementary Table SM2.9: Covariate distributions by censoring status in first year

	Censored (N=88)	Not Censored (N=791)	P-value
Age at study entry, years			
Mean (SD)	70.75 (10.71)	68.86 (8.71)	0.113
Self-identified race			
White	64 (73%)	640 (81%)	0.0924
Black	24 (27%)	151 (19%)	
Disease state at enrollment			
CRPC	42 (48%)	264 (33%)	0.0104
mHSPC	46 (52%)	527 (67%)	
Highest education level at baseline			
Less than College	25 (28%)	164 (21%)	0.263
Some College or Bachelor's Degree	22 (25%)	247 (31%)	
Vocational School/Program	0 (0%)	12 (2%)	
Graduate Degree	38 (43%)	352 (45%)	
Other	3 (3%)	16 (2%)	
Marital status at baseline			
Married	51 (58%)	589 (74%)	<0.001

	Censored (N=88)	Not Censored (N=791)	P-value
In a Civil Partnership	2 (2%)	20 (3%)	
Widowed	11 (12%)	30 (4%)	
Divorced/Separated	19 (22%)	102 (13%)	
Never Married	5 (6%)	50 (6%)	
Employment status at baseline			
Retired	60 (68%)	434 (55%)	<0.001
Working Full-Time	11 (12%)	237 (30%)	
Working Part-Time	3 (3%)	66 (8%)	
Unemployed	4 (5%)	24 (3%)	
Disabled	10 (11%)	30 (4%)	
Member of national military at baseline			
Yes, currently or previously	31 (35%)	253 (32%)	0.619
No, I have never served in the national military	57 (65%)	538 (68%)	
Prostatectomy or biopsy gleason score			
6 or less	5 (6%)	31 (4%)	0.469
7	23 (26%)	235 (30%)	
8	12 (14%)	144 (18%)	
9-10	48 (55%)	381 (48%)	
First on-study PSA (ng/mL)			
Mean (SD)	191.41 (446.16)	89.42 (459.39)	0.045
Completeness of case			
Complete	45 (51%)	419 (53%)	0.83
Incomplete	43 (49%)	372 (47%)	

In this analysis, we did see evidence for differences in demographic and clinical covariates for those who were censored compared to those who weren't. Specifically, marital status and employment status at baseline are highly different between these groups, and race, disease state at enrollment, and first on-study PSA are also quite different between these groups. **Overall, there are differences between those who are censored in the first year of follow-up and those who remain on-study.**

Rationale behind our choice of longitudinal model

For our main analyses, we chose linear mixed effects models to determine the association between race and the EORTC quality of life scale scores. Two considerations for deciding between linear mixed effects models (LMEs) and generalized estimating equation models (GEEs) are 1) how each of the approaches handles missing data, and 2) how each of the approaches handles death as a competing event.

In a standard longitudinal analysis of quality of life without special considerations for death, the model implicitly assumes that quality of life trajectory continues on after death. This, of course, is not true. Kurland et al described using GEEs with an independent working correlation to account for death in a longitudinal analysis of quality of life interested in drawing conclusions about quality of life for the survivors who made it to each timepoint.(6) Using GEEs in this way would require additional adjustment for missingness (both non-monotone missingness and censoring). Recent methods explore the use of inverse probability weighting of GEEs to account for non-monotonicity in missing data.(7) These methods require specifying a model for each pattern of missingness; with five timepoints and 30 patterns of missingness, we believe this approach would be too methodologically complex considering the lack of strong evidence we saw regarding predictors of non-monotonicity described in the above analyses.

LMEs provide correct inference under the missing at random assumption without additional adjustment, accounting for both non-monotonic missingness as well as missingness due to censoring; however, LMEs do not naturally account for death as a competing event as described above. In our adjusted model, we include race, age, and disease state at enrollment as covariates in the model. Thus, our LMEs are assuming that the questionnaires are missing at random based on these three observed variables. This seems reasonable for the non-monotonic missing questionnaires from those who are on-study; however, this seems less plausible for accounting for missingness due to censoring. For example, distributions of marital status at enrollment and employment status at enrollment are significantly different between

those who are censored and those who remain on-study. We do not want to adjust for these variables in our longitudinal models as these are likely mediators of the race-quality of life association and thus would remove some of the overall effect of race that we are interested in here.

To assess how our results might be affected by the differences in those who are censored and those who are not censored, and also to gain insight into how not directly accounting for death might affect the results, we conducted a sensitivity analysis including only those who were never censored in the first year of follow up. The results for this analysis are shown in **Supplementary Table 2.4,** with the intercept from the crude model and all other coefficients and random effect variations from the adjusted model as presented in the main paper**.**

Supplementary Table 2.4 (repeated from above): Longitudinal analysis results from sensitivity analysis excluding individuals who were censored due to being off-study in the first year

	Intercept Mean (95% CI)	Race Coefficient Mean (95% CI)	Month Coefficient Mean (95% CI)	Interaction Coefficient Mean (95% CI)	SD of subject random effect	SD of site random effect
Global Quality of Life (QL)	72.3 (70.5, 74.2)	-1.4 (-4.9, 2.2)	**-0.4 (-0.5, -0.2)**	-0.1 (-0.3, 0)	15.1	2.4
Functioning Scales						
Physical (PF)	85.8 (83.6, 88.1)	**-3.4 (-6.7, 0.2)**	**-0.6 (-0.7, -0.5)**	**-0.4 (-0.5, -0.3)**	14.2	3.8
Emotional (EF)	82.1 (80.2, 84.0)	**4.7 (1.6, 7.8)**	-0.1 (-0.2, 0)	**0.2 (0.1, 0.4)**	13.2	3.2
Social (SF)	81.8 (79.2, 84.3)	0.8 (-3.3, 4.8)	**-0.3 (-0.4, -0.1)**	0 (-0.1, 0.2)	15.8	4.8
Role (RF)	82.5 (79.8, 85.2)	-2.2 (-6.7, 2.3)	**-0.7 (-0.8, -0.5)**	-0.1 (-0.3, 0)	17.6	4.6
Cognitive (CF)	85.0 (83.0, 87.0)	0.1 (-3.1, 3.4)	**-0.3 (-0.5, -0.2)**	0 (-0.2, 0.1)	13.6	3.5
Symptom Scales						
Fatigue (FA)	29.0 (26.4, 31.5)	-1.0 (-5.0, 3.1)	**0.6 (0.4, 0.7)**	0 (-0.1, 0.2)	16.8	4.7
Nausea/vomiting (NV)	3.6 (2.9, 4.3)	**2.2 (0.5, 3.9)**	0 (-0.1, 0.1)	**-0.1 (-0.2, -0.1)**	6.0	0.0
Pain (PA)	17.6 (15.1, 20.1)	4.0 (-0.3, 8.2)	**0.4 (0.2, 0.6)**	**-0.3 (-0.4, -0.1)**	17.6	4.5
Dyspnea (DY)	13.3 (11.0, 15.7)	1.8 (-2.3, 5.9)	**0.5 (0.4, 0.7)**	0.2 (0, 0.4)	17.3	3.5
Sleep (SL)	29.3 (26.6, 32.0)	**-9.0 (-13.8, -4.2)**	0.1 (-0.1, 0.3)	**-0.3 (-0.5, -0.1)**	19.7	4.0
Appetite (AP)	9.4 (7.6, 11.1)	3.4 (-0.1, 6.8)	0.1 (-0.1, 0.2)	0.1 (-0.1, 0.2)	13.2	2.1
Constipation (CO)	11.6 (9.9, 13.3)	**6.9 (3.2, 10.6)**	**0.2 (0.1, 0.4)**	0.2 (0, 0.3)	14.4	0.9
Diarrhea (DI)	10.0 (8.1, 11.8)	-2.0 (-5.1, 1.2)	0.1 (-0.1, 0.2)	-0.1 (-0.2, 0)	11.5	3.1
Financial insecurity (FI)	15.4 (12.8, 18.0)	**5.2 (0.8, 9.7)**	-0.1 (-0.3, 0)	**-0.6 (-0.8, -0.4)**	19.6	4.4

All directions and magnitudes of coefficients as well as statistical significance for each of the scales are nearly identical to the results for the entire study population presented in the main text; the only exception is the race coefficient for the pain scale, which is in the same direction and magnitude as the whole study population but does not reach statistical significance here. Thus, we believe that even though the individuals who are censored vs. not censored are qualitatively different based on their baseline covariate distributions, this is not substantially affecting the results that we see.

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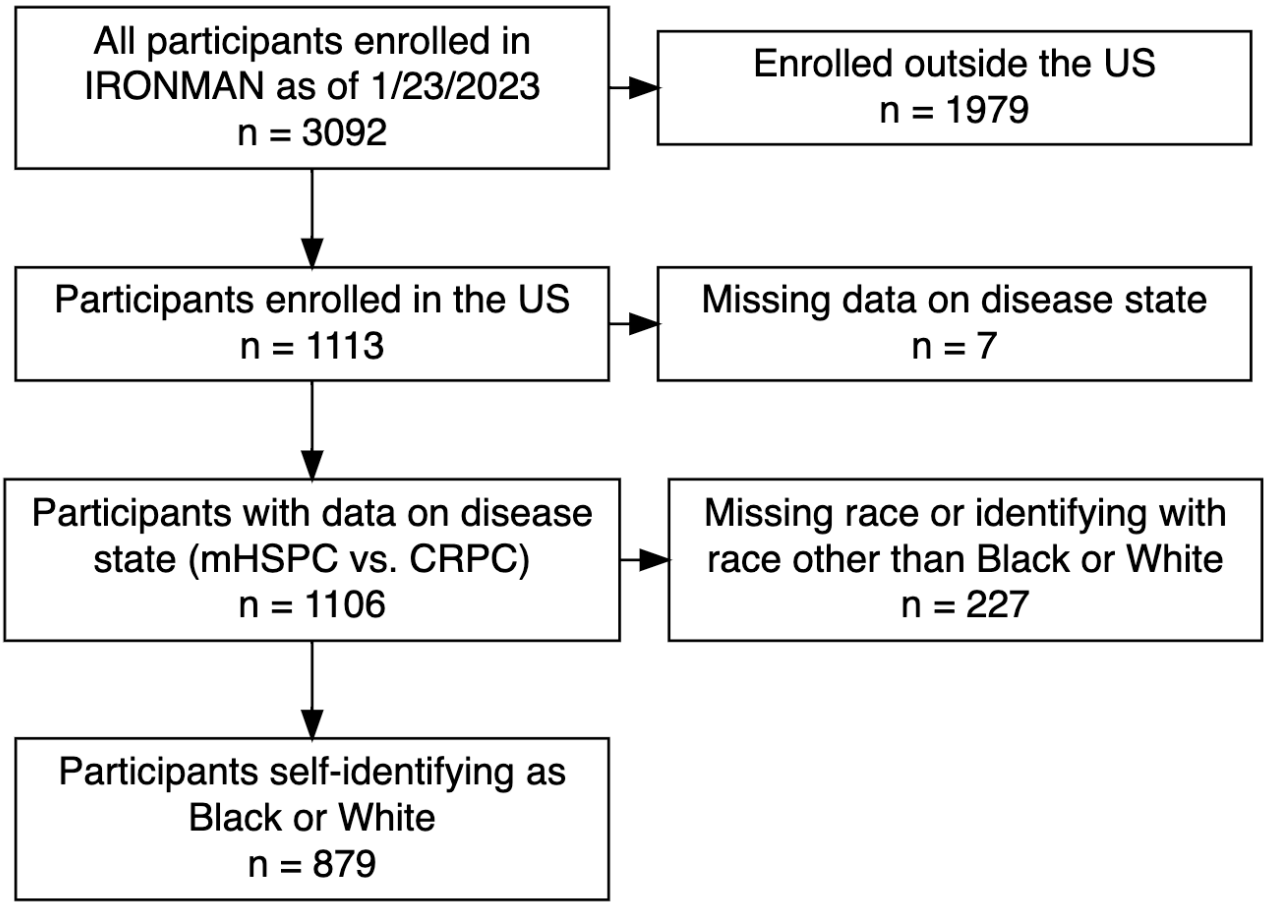
Appendix 3: Supplementary Material for Chapter 3

Supplementary Figure 3.1: Selection of study participants



IRONMAN = International Registry for Men with Advanced Prostate Cancer. mHSPC = metastatic hormone sensitive prostate cancer. CRPC = castration resistant prostate cancer

Supplementary Table 3.1: Study sites for IRONMAN participants by race (N = 38 sites)

	White (N=704)	Black (N=175)
Baylor College of Medicine	6 (0.9%)	10 (5.7%)
Chesapeake Urology Associates	6 (0.9%)	5 (2.9%)
Columbia University	4 (0.6%)	2 (1.1%)
Dana-Farber Cancer Institute	41 (5.8%)	3 (1.7%)
Delnor Cancer Center	20 (2.8%)	1 (0.6%)
Doylestown Health	14 (2.0%)	0 (0%)
Duke Cancer Network	5 (0.7%)	6 (3.4%)
Duke Comprehensive Cancer Center	55 (7.8%)	11 (6.3%)
Kishwaukee Cancer Center	1 (0.1%)	0 (0%)
Memorial Sloan Kettering Cancer Center	65 (9.2%)	8 (4.6%)
Memphis VA Medical Center	4 (0.6%)	6 (3.4%)
Moffitt Cancer Center	3 (0.4%)	0 (0%)
Oregon Health and Sciences Cancer Center	24 (3.4%)	0 (0%)
Ralph H. Johnson VA Medical Center	10 (1.4%)	5 (2.9%)
Reading Health System	9 (1.3%)	2 (1.1%)
Robert H. Lurie Comprehensive Cancer Center Northwestern University	6 (0.9%)	0 (0%)
Roswell Park Cancer Institute	5 (0.7%)	1 (0.6%)
Sidney Kimmel Comprehensive Cancer Center	7 (1.0%)	6 (3.4%)
Thomas Jefferson University	3 (0.4%)	1 (0.6%)
Tulane University	53 (7.5%)	8 (4.6%)
University of Alabama-Birmingham	4 (0.6%)	3 (1.7%)
University of California Los Angeles	7 (1.0%)	0 (0%)
University of California San Diego	31 (4.4%)	2 (1.1%)
University of Chicago	20 (2.8%)	12 (6.9%)
University of Illinois at Chicago	4 (0.6%)	1 (0.6%)
University of Michigan	27 (3.8%)	4 (2.3%)
University of Mississippi Medical Center	3 (0.4%)	5 (2.9%)
University of North Carolina	31 (4.4%)	8 (4.6%)
University of Virginia	113 (16.1%)	15 (8.6%)
University of Washington	39 (5.5%)	1 (0.6%)
University of Wisconsin	8 (1.1%)	0 (0%)
Warrenville Cancer Center	1 (0.1%)	0 (0%)

	White (N=704)	Black (N=175)
Wayne St. University Karmanos Cancer Institute	24 (3.4%)	28 (16.0%)
Weill Cornell Medical Center	44 (6.3%)	4 (2.3%)
Winship Cancer Institute Emory University	7 (1.0%)	9 (5.1%)
Durham VA Medical Center	0 (0%)	5 (2.9%)
Fox Chase Cancer Center - Temple Health	0 (0%)	1 (0.6%)
New York-Presbyterian Brooklyn Methodist Hospital	0 (0%)	2 (1.1%)

Supplementary Table 3.2: Number of participants receiving each therapy category between 3 months prior to enrollment and any time after enrollment (N=19 therapy categories)

	Overall (N=879)
ADT	782 (88.9%)
AR Signaling Inhibitor	591 (67.2%)
Chemotherapy	214 (24.3%)
Immunotherapy	74 (8.0%)
Radiopharmaceuticals	57 (6.5%)
PARP	23 (2.6%)
Multi-kinase Inhibitor	6 (0.7%)
Immunotherapy/Placebo	5 (0.6%)
mTOR kinase/DNA-PK Inhibitor	5 (0.6%)
CDK Inhibitor	2 (0.2%)
TGF-ßRI kinase Inhibitor	2 (0.2%)
CDK Inhibitor/Placebo	1 (0.1%)
EZH2 Inhibitor	1 (0.1%)
GR Antagonist	1 (0.1%)
PARP/Placebo	1 (0.1%)
PI3K Inhibitor	1 (0.1%)
PLK1 Inhibitor	1 (0.1%)
SHP2 Inhibitor	1 (0.1%)
α/β Tubulin Inhibitor	1 (0.1%)

Note: participants can fall into more than one group and often are receiving multiple of these therapy categories at the same time

Supplementary Table 3.3: Clinical disease characteristics stratified by self-reported race

	White (N=704)	Black (N=175)
Age at study entry, years		
Mean (SD)	69.5 (8.9)	67.2 (8.7)
Disease state at enrollment		
mHSPC	463 (66%)	110 (63%)
mCRPC	212 (30%)	61 (35%)
nmCRPC	29 (4%)	4 (2%)
De novo metastatic disease at enrollment		
Yes	294 (68%)	70 (71%)
No	137 (32%)	28 (29%)
Missing	n = 273	n = 77
Location of metastases at enrollment		
No metastases at baseline	29 (7%)	4 (3%)
Lymph nodes only	36 (9%)	15 (13%)
Bone +/- lymph nodes only	245 (63%)	77 (66%)
Other soft tissue metastases present	80 (21%)	21 (18%)
Missing	n = 314	n = 58
Prostatectomy or biopsy Gleason grade		
6 or less	26 (5%)	3 (2%)
7	163 (28%)	45 (34%)
8	106 (18%)	20 (15%)
9-10	278 (49%)	63 (48%)
Missing	n = 131	n = 44
First on-study PSA (ng/mL)		
Mean (SD)	88.6 (484.8)	156.9 (396.3)
Missing	n = 33	n = 8

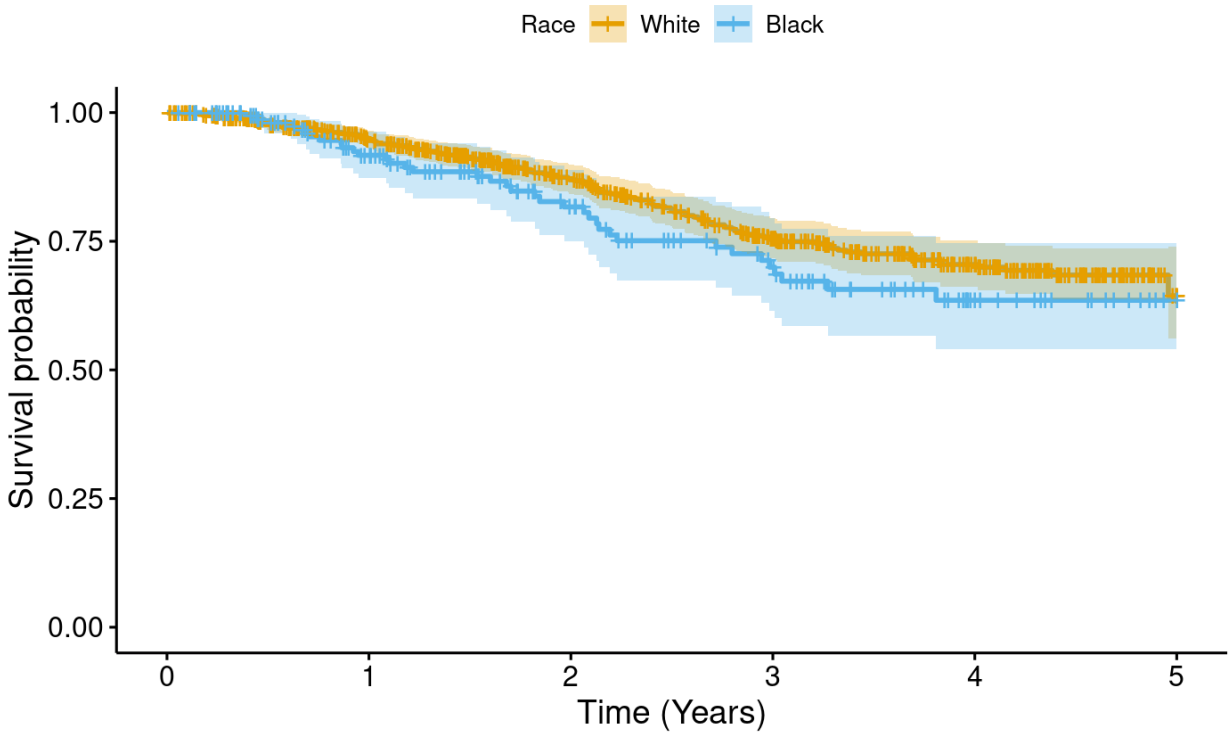
Supplementary Table 3.4: Correlation coefficients between baseline pain scale scores

	EORTC Pain Scale	Average Pain	Worst Pain	Bone Pain
EORTC Pain Scale	1.00	0.75	0.80	0.56
Average Pain	0.75	1.00	0.87	0.59
Worst Pain	0.80	0.87	1.00	0.58
Bone Pain	0.56	0.59	0.58	1.00

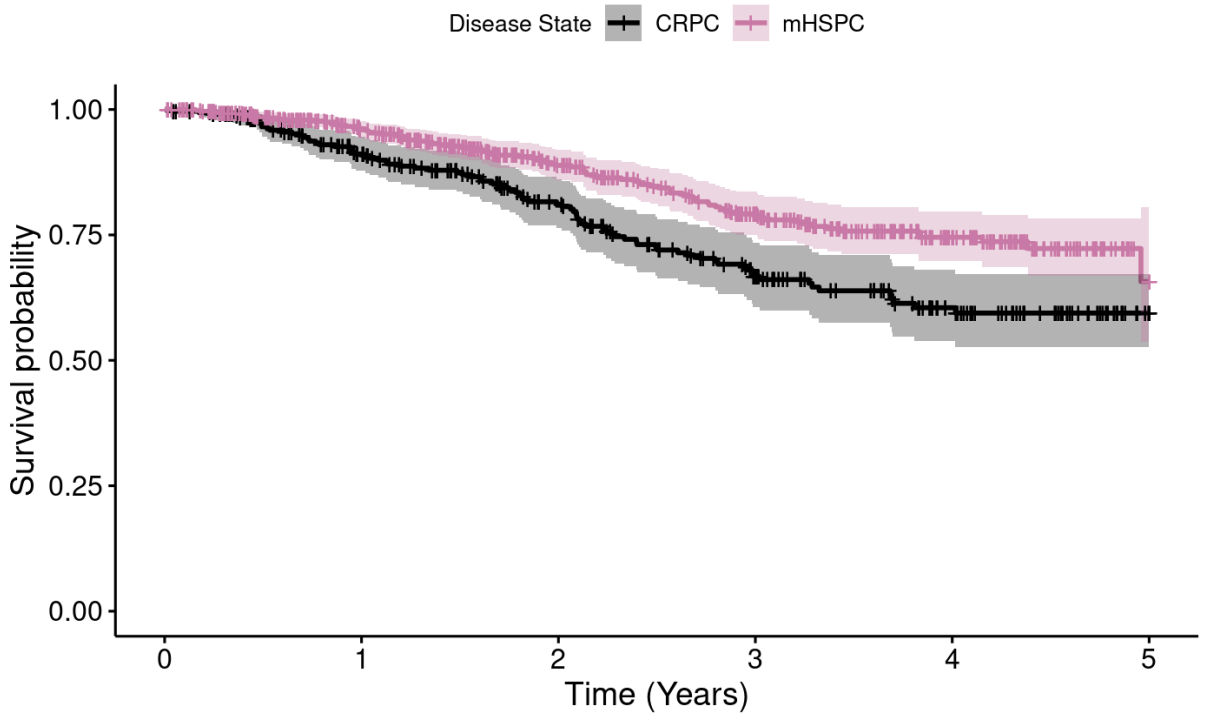
Supplementary Table 3.5: Reasons for being off-study by self-reported race

Off-study reason	White participants (N=704)	Black participants (N=175)
Death	137 (19.5%)	37 (21.4%)
Withdrawal by participant	59 (8.4%)	13 (7.4%)
Lost to follow-up	31 (4.4%)	10 (5.7%)
Study termination	26 (3.7%)	5 (2.9%)
Clinical deterioration	22 (3.1%)	9 (5.1%)

Supplementary Figure 3.2: Kaplan-Meier survival curve by self-reported race



Supplementary Figure 3.3: Kaplan-Meier survival curve by disease state at study enrollment



Supplementary Table 3.6: 80th percentile survival and 95% confidence intervals for each category of pain at study enrollment

Pain scale	No pain	A little pain	Quite a bit of pain
EORTC pain scale	3.01 (2.50, 3.83)	2.19 (1.90, 2.57)	1.60 (0.99, 2.66)
Average pain rating	2.81 (2.41, 3.69)	2.40 (2.09, 3.32)	1.82 (1.08, 2.70)
Worst pain rating	2.84 (2.57, 3.83)	2.34 (2.06, 2.90)	1.93 (1.60, 3.29)
Bone pain presence	2.81 (2.50, 3.69)	2.08 (1.66, 2.61)	1.60 (0.67, 3.83)

Supplementary Methods

This section describes our exploration of missing data in two parts: 1) missing individual variables on completed questionnaires, and 2) missing entire questionnaires, particularly an exploration of censoring as IRONMAN is ongoing.

Missing individual variables on completed questionnaires

We began by exploring missing data on questionnaires that were completed by the participants. The completion of each of the 5 pain questions on the completed questionnaires are shown in **Supplementary Table SM3.1**.

Supplementary Table SM3.1: Missingness of individual pain questions on completed questionnaires

	EORTC1	EORTC2	Average pain	Worst pain	Bone pain
Total completed questionnaires	6150	6150	6150	6150	3331
Total missing	42	59	99	102	112

Missingness of pain questions on completed questionnaires was small (~3% for the bone pain question to less than 1% for the EORTC questions). We used multiple imputation by chained equations to create imputed datasets for the missing pain questions. As we were interested in the scale score for the EORTC pain questions rather than the individual questions, we calculated the EORTC scale score where both questions were complete and imputed the scale scores.(1) We began by making a long dataset where each row represented a single timepoint for one individual. As we only wanted to impute the missing pain questions on completed questionnaires, we set the pain scales on missing full questionnaires to a missing indicator value (-250 for the EORTC scale, -25 for the average and worst pain scales, and -10 for the bone pain question). The missing indicator values needed to be numeric and also outside of the range of each scale so as to not bias the results. We then converted to a wide

dataset with one row per individual to preserve clustering by participant during the imputation process.

MICE was conducted on the wide dataset using the following variables(2): participant ID, race, marital status, highest education attained, employment status, military status, metastatic status at baseline, study site ID, disease state at enrollment, age, PSA, Gleason score, de novo metastatic disease, location of metastases, type of health center at which the participant received care, year of enrollment, death status, and time on study. We used the MICE method of classification and regression trees and constrained the outcome variable imputations to be between the possible bounds of the range for each scale (0-100 for the EORTC scale, 1-10 for average and worst pain, and 0-4 for bone pain). We created 10 imputed datasets using 10 iterations for each imputation to stabilize. After the MICE procedure, we had full pain scale data for completed questionnaires and full covariate data for all participants. We then converted back to a long dataset and returned the numeric indicator values back to missing.

We conducted sensitivity analyses using different values for the missing indicator to determine how robust our results of the longitudinal analysis were to the chosen value. The results of these sensitivity analyses for each pain scale in the baseline Cox model are shown in **Supplementary Tables SM3.2-SM3.5** below**.** The most negative values were chosen for the final analysis as they were the furthest from the scale of the pain questions.

Supplementary Table SM3.2: Baseline EORTC pain scale Cox model results from sensitivity analysis for missing indicator values during MICE procedure (see Supplemental methods text for more information)

Missing Indicator Value	HR (95% CI)
-250	1.104 (1.034, 1.173)
-200	1.104 (1.034, 1.172)
-150	1.102 (1.033, 1.170)
-100	1.102 (1.032, 1.171)

EORTC pain scale ranged from 0-100. Missing indicators for other scales during the imputation procedure were -25 (average and worst pain) and -10 (bone pain).

Supplementary Table SM3.3: Baseline average pain scale Cox model results from sensitivity analysis for missing indicator values during MICE procedure (see Supplemental methods text for more information)

Missing Indicator Value	HR (95% CI)
-25	1.191 (1.085, 1.319)
-20	1.195 (1.089, 1.313)
-15	1.190 (1.080, 1.314)
-10	1.191 (1.086, 1.318)

Average pain scale ranged from 1-10. Missing indicators for other scales during the imputation procedure were -250 (EORTC pain scale), -25 (worst pain), and -10 (bone pain).

Supplementary Table SM3.4: Baseline worst pain scale Cox model results from sensitivity analysis for missing indicator values during MICE procedure (see Supplemental methods text for more information)

Missing Indicator Value	HR (95% CI)
-25	1.162 (1.078, 1.252)
-20	1.161 (1.083, 1.245)
-15	1.165 (1.084, 1.252)
-10	1.161 (1.083, 1.244)

Worst pain scale ranged from 1-10. Missing indicators for other scales during the imputation procedure were -250 (EORTC pain scale), -25 (average pain), and -10 (bone pain).

Supplementary Table SM3.5: Baseline bone pain scale Cox model results from sensitivity analysis for missing indicator values during MICE procedure (see Supplemental methods text for more information)

Missing Indicator Value	HR (95% CI) – some vs. none	HR (95% CI) – a lot vs. none
-10	1.608 (1.097, 2.374)	2.472 (1.440, 4.216)
-9	1.611 (1.101, 2.373)	2.475 (1.439, 4.216)
-8	1.609 (1.108, 2.366)	2.477 (1.435, 4.218)
-7	1.613 (1.118, 2.372)	2.488 (1.450, 4.228)

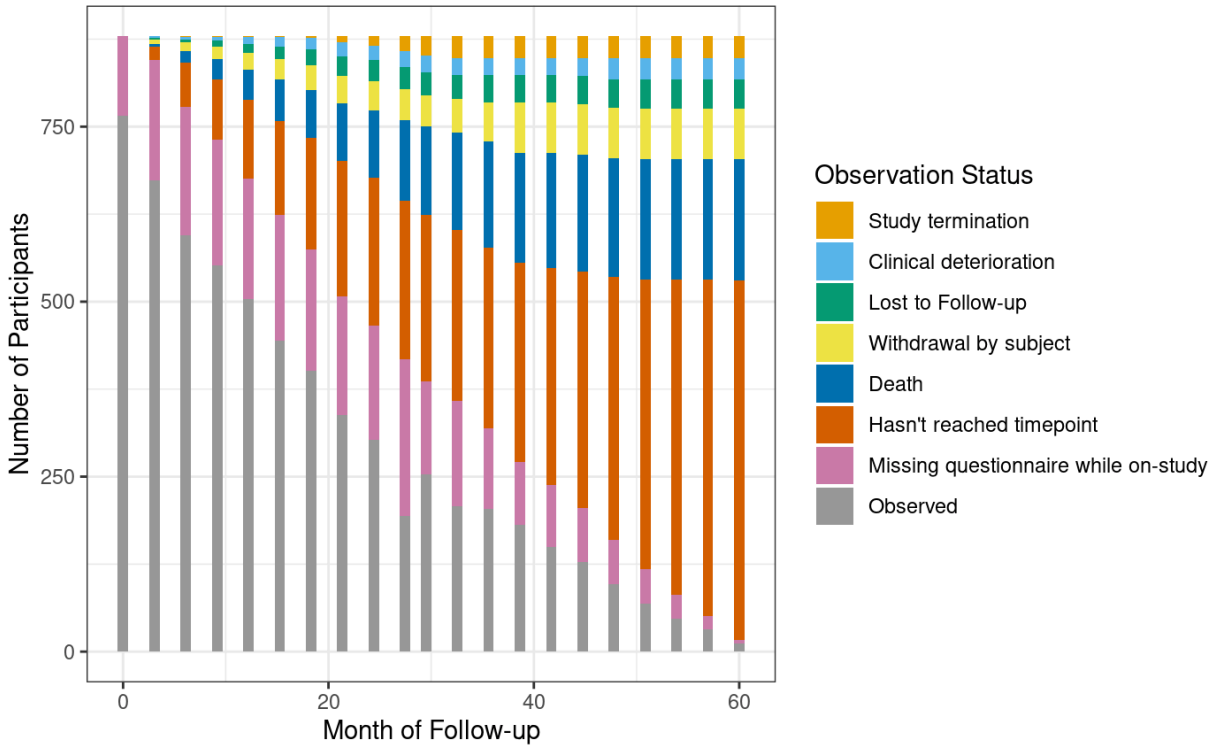
Bone pain scale ranged from 0-4. Missing indicators for other scales during the imputation procedure were -250 (EORTC pain scale) and -25 (average and worst pain).

Missing entire questionnaires

To assess missingness of entire questionnaires, we classified questionnaires into four groups: 1) completed, 2) missing while on-study, 3) censored due to death, withdrawal, etc, and 4) censored due to not accruing enough person-time on-study to complete the questionnaire (as IRONMAN enrollment is ongoing).

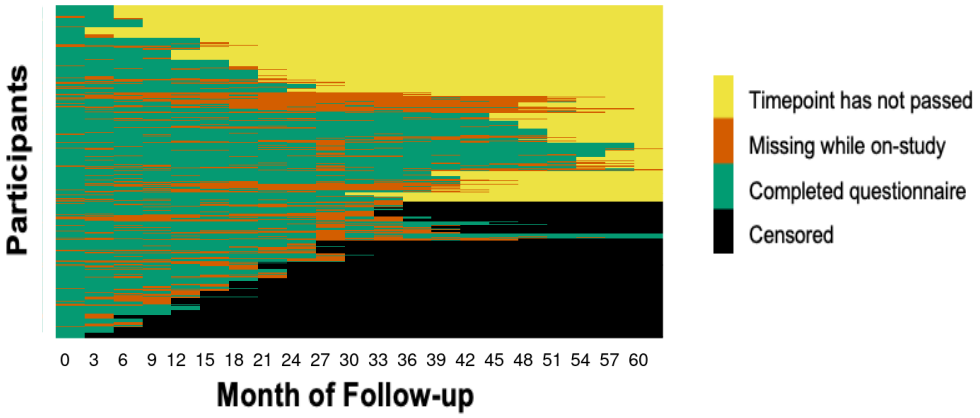
To visualize the longitudinal missingness in the data, we created **Supplementary Figure SM3.1** and **Supplementary Figure SM3.2** below. Supplementary Figure SM1 shows the observation status of each questionnaire/reason for being off-study for each participant over five years of follow-up. 345 participants (39%) were off-study during follow-up.

Supplementary Figure SM3.1: Proportion of the observation status for whole questionnaires at each timepoint



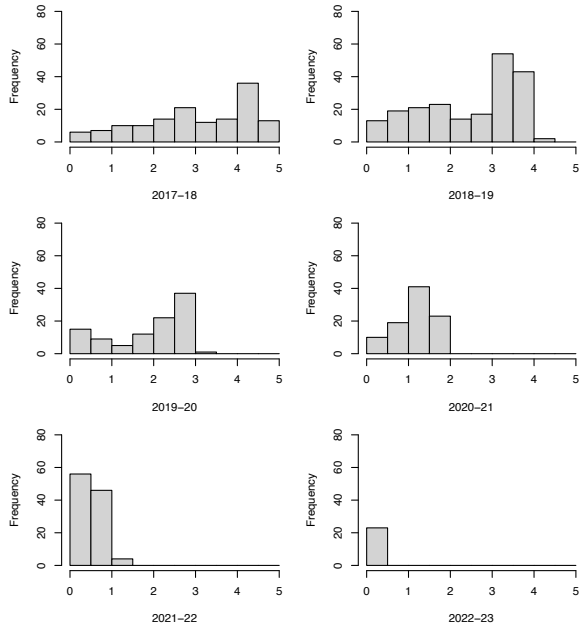
Supplementary Figure SM2 shows the longitudinal missing data patterns for each study participant according to the four categories listed above.

Supplementary Figure SM3.2: Longitudinal missing data patterns for whole questionnaires for each participant



As IRONMAN enrollment is ongoing, there have been numerous protocol changes, and a global pandemic occurred in the middle of study enrollment, we wanted to assess the role of censoring in these data. **Supplementary Figure SM3.3** below shows the distribution of censoring times by year of enrollment (excluding participants who died). We see that late censoring occurs in participants who were enrolled early on, and early censoring is primarily among participants who were recently enrolled and haven't yet accrued person-time sufficient for long-term follow-up. From this, we determined that censoring likely isn't impacting our results substantially unless there are substantial cohort differences by enrollment year.

Supplementary Figure SM3.3: distribution of censoring times by year of enrollment (excluding death)



To explore potential cohort differences by enrollment year, we assessed differences in demographic/clinical variables, study site, and baseline pain scores by enrollment year. We categorized enrollment year as a binary variable with one level representing enrollment in the first half of the study (June 2017 – June 2020), and the other level representing enrollment in the second half of the study (July 2020 – February 2023).

Supplementary Table SM3.6 below shows differences in demographic and clinical variables by enrollment year. There are some differences by enrollment year, including for disease state, education, employment status, and type of health center at which the participant received care.

Supplementary Table SM3.6: Demographic and clinical characteristics stratified by enrollment year

	Enrolled 2017-2020 (N=603)	Enrolled 2020-2023 (N=276)	P-value
Age at study entry, years			
Mean (SD)	68.8 (9.1)	69.6 (8.6)	0.171
Self-identified race			
White	494 (82%)	210 (76%)	0.0548
Black	109 (18%)	66 (24%)	
Disease state at enrollment			
mHSPC	363 (60%)	210 (76%)	<0.001
mCRPC	215 (36%)	58 (21%)	
nmCRPC	25 (4%)	8 (3%)	
Highest education level at baseline			
Less than College	44 (24%)	3 (4%)	<0.001
Some College or Bachelor's Degree	82 (45%)	3 (4%)	
Vocational School/Program	1 (1%)	2 (3%)	
Graduate Degree	50 (28%)	60 (88%)	
Other	4 (2%)	0 (0%)	
Missing	n = 422	n = 208	
Marital status at baseline			
Married	443 (75%)	190 (69%)	0.102
In a Civil Partnership	17 (3%)	5 (2%)	
Widowed	27 (5%)	14 (5%)	
Divorced/Separated	69 (12%)	50 (18%)	
Never Married	38 (6%)	16 (6%)	
Missing	n = 9	n = 1	
Employment status at baseline			
Retired	330 (55%)	160 (58%)	0.0731
Working Full-Time	177 (30%)	68 (25%)	
Working Part-Time	47 (8%)	22 (8%)	
Unemployed	22 (4%)	6 (2%)	
Disabled	20 (3%)	19 (7%)	
Missing	n = 7	n = 1	
Member of national military at baseline			
Yes, currently or previously	126 (31%)	93 (34%)	0.381
No, I have never served in the national military	283 (69%)	178 (66%)	

	Enrolled 2017-2020 (N=603)	Enrolled 2020-2023 (N=276)	P-value
Missing	n = 194	n = 5	
Prostatectomy or biopsy gleason score			
6 or less	23 (5%)	6 (3%)	0.337
7	145 (29%)	63 (31%)	
8	84 (17%)	42 (21%)	
9-10	251 (50%)	90 (45%)	
Missing	n = 100	n = 75	
First on-study PSA (ng/mL)			
Mean (SD)	101.5 (450.2)	104.0 (514.1)	0.948
Missing	n = 5	n = 36	
De novo metastatic disease at baseline			
Yes	244 (71%)	120 (65%)	0.141
No	99 (29%)	66 (35%)	
Missing	n = 260	n = 90	
Location of metastases at baseline			
No metastases at baseline	25 (7%)	8 (6%)	0.658
Lymph nodes only	37 (10%)	14 (10%)	
Bone +/- lymph nodes only	229 (62%)	93 (67%)	
Other soft tissue metastases present	78 (21%)	23 (17%)	
Missing	n = 234	n = 138	
Type of health center			
Clinic	28 (5%)	9 (3%)	<0.001
Hospital	82 (14%)	64 (23%)	
NCI	493 (82%)	173 (63%)	
VA	0 (0%)	30 (11%)	

Supplementary Table SM3.7 below shows differences in site accrual by enrollment year. NCI-designated health centers tended to enroll fewer participants in the second half of the study (likely due to clinical trial enrollment changes during the COVID pandemic) and sites added as participating centers later (eg the Ralph H. Johnson VA Medical Center) only enrolled participants in the second half of the study.

Supplementary Table SM3.7: Site enrollment stratified by enrollment year

	Enrolled 2017-2020 (N=603)	**Enrolled 2020-2023 (N=276)**
Baylor College of Medicine	16 (2.7%)	0 (0%)
Chesapeake Urology Associates	7 (1.2%)	4 (1.4%)
Columbia University	5 (0.8%)	1 (0.4%)
Dana-Farber Cancer Institute	38 (6.3%)	6 (2.2%)
Delnor Cancer Center	4 (0.7%)	17 (6.2%)
Doylestown Health	14 (2.3%)	0 (0%)
Duke Comprehensive Cancer Center	62 (10.3%)	4 (1.4%)
Memorial Sloan Kettering Cancer Center	72 (11.9%)	1 (0.4%)
Oregon Health and Sciences Cancer Center	9 (1.5%)	15 (5.4%)
Reading Health System	7 (1.2%)	4 (1.4%)
Robert H. Lurie Comprehensive Cancer Center Northwestern University	6 (1.0%)	0 (0%)
Roswell Park Cancer Institute	6 (1.0%)	0 (0%)
Sidney Kimmel Comprehensive Cancer Center	12 (2.0%)	1 (0.4%)
Thomas Jefferson University	4 (0.7%)	0 (0%)
Tulane University	52 (8.6%)	9 (3.3%)
University of Alabama-Birmingham	7 (1.2%)	0 (0%)
University of California Los Angeles	6 (1.0%)	1 (0.4%)
University of California San Diego	13 (2.2%)	20 (7.2%)
University of Chicago	24 (4.0%)	8 (2.9%)
University of Michigan	31 (5.1%)	0 (0%)
University of North Carolina	35 (5.8%)	4 (1.4%)
University of Virginia	61 (10.1%)	67 (24.3%)

	Enrolled 2017-2020 (N=603)	Enrolled 2020-2023 (N=276)
University of Washington	35 (5.8%)	5 (1.8%)
University of Wisconsin	4 (0.7%)	4 (1.4%)
Wayne St. University Karmanos Cancer Institute	31 (5.1%)	21 (7.6%)
Weill Cornell Medical Center	26 (4.3%)	22 (8.0%)
Winship Cancer Institute Emory University	16 (2.7%)	0 (0%)
Duke Cancer Network	0 (0%)	11 (4.0%)
Durham VA Medical Center	0 (0%)	5 (1.8%)
Fox Chase Cancer Center - Temple Health	0 (0%)	1 (0.4%)
Kishwaukee Cancer Center	0 (0%)	1 (0.4%)
Memphis VA Medical Center	0 (0%)	10 (3.6%)
Moffitt Cancer Center	0 (0%)	3 (1.1%)
New York-Presbyterian Brooklyn Methodist Hospital	0 (0%)	2 (0.7%)
Ralph H. Johnson VA Medical Center	0 (0%)	15 (5.4%)
University of Illinois at Chicago	0 (0%)	5 (1.8%)
University of Mississippi Medical Center	0 (0%)	8 (2.9%)
Warrenville Cancer Center	0 (0%)	1 (0.4%)

Supplementary Table SM3.8 below shows differences in baseline pain scores by enrollment year. No statistically significant differences were noted in pain questions at study enrollment based on the enrollment year of the participant.

Supplementary Table SM3.8: Baseline pain scale scores stratified by enrollment year

	Enrolled 2017-2020 (N=603)	Enrolled 2020-2023 (N=276)	P
How often have you had pain in the past week?			
1 - Not at all	252 (49%)	117 (48%)	0.384
2 - A little	192 (37%)	81 (33%)	
3 - Quite a bit	50 (10%)	30 (12%)	
4 - Very much	22 (4%)	15 (6%)	
Missing	n = 87	n = 33	
How often did pain interfere with your daily activities in the past week?			

	Enrolled 2017-2020 (N=603)	Enrolled 2020-2023 (N=276)	P
1 - Not at all	341 (66%)	143 (59%)	0.0938
2 - A little	128 (25%)	65 (27%)	
3 - Quite a bit	27 (5%)	23 (10%)	
4 - Very much	19 (4%)	11 (5%)	
Missing	n = 88	n = 34	
EORTC pain scale (0-100)			
Mean (SD)	19.33 (24.59)	22.73 (27.37)	0.101
Missing	n = 89	n = 34	
Rate your pain at its worst in the last 24 hours (1-10)			
Mean (SD)	2.63 (2.13)	2.75 (2.34)	0.505
Missing	n = 110	n = 34	
Rate your average pain (1-10)			
Mean (SD)	2.35 (1.74)	2.52 (1.90)	0.236
Missing	n = 110	n = 34	
How often have you had bone pain in the past week?			
0 - Not at all	300 (61%)	134 (56%)	0.19
1 - A little bit	106 (22%)	57 (24%)	
2 - Somewhat	43 (9%)	16 (7%)	
3 - Quite a bit	31 (6%)	23 (10%)	
4 - Very much	10 (2%)	9 (4%)	
Missing	n = 113	n = 37	

Taken together, we believe that there are likely some cohort differences depending on year of enrollment that could affect our results. As such, we stratified the baseline hazard of our Cox proportional hazards in both the baseline and longitudinal settings by year of enrollment (as a categorical variable from 1 to 6 representing each year of enrollment).

References

1. EORTC Data Center. EORTC QLQ-C30 Scoring Manual. 2001;3rd edition.
2. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res. 2011;20(1):40–9.

Appendix 4: Glossary of Technical Terms

Advanced prostate cancer: cancer that has spread outside of the prostate gland (mHSPC) and/or cancer that is resistant to hormone therapy (CRPC).

Castration resistant prostate cancer (CRPC): cancer that is either only in the prostate gland or has spread throughout the body that does not respond to hormone therapy. Newer and more aggressive treatment options are typically used.

Cox proportional hazards model: a method used to determine the relationship between a variable and the risk of death after accounting for other variables that might bias the results

Joint longitudinal survival models: a method used to determine the relationship between the longitudinal trend of a variable and the risk of death after accounting for other variables that might bias the results

Kaplan-Meier estimates: a method used to create a graph that shows the survival probability for individuals in a group over time

Linear mixed effects model: a mathematical equation that allows researchers to determine the relationship between a variable of interest and an outcome of interest. This type of equation is used for continuous outcomes and allows us to group data over time within individuals (ie one person filling out a questionnaire at 5 timepoints) and group individuals within sites at which they receive care.

Localized prostate cancer: cancer that is only present inside the prostate gland and has not spread to other parts of the body. Typically treated with surgery and/or radiation, sometimes also treated with hormone therapy.

Logistic-normal mixed effects model: a mathematical equation that allows researchers to determine the relationship between a variable of interest and an outcome of interest. This type of equation is used for binary outcomes and allows us to group together patients based on the clinic at which they receive care.

Metastatic hormone-sensitive prostate cancer (mHSPC): cancer that has spread outside of the prostate gland but is still responsive to hormone therapy as a treatment.

Multiple imputation by chained equations (MICE): a way to fill in missing variables in a dataset by comparing people in the dataset. If an individual in a dataset is missing data on age, for example, MICE would find someone else in the dataset who looks similar to that person (ie a person of the same gender with the same disease state, education level, marital status, etc) and fill in the first missing person's data with the second person's age.

Non-monotone missingness: a pattern of missingness in which a study participant completes a questionnaire at one timepoint, misses the next timepoint, and then comes back to fill in the questionnaire at the third timepoint.

Parametric bootstrapping: a way to use the data available to create many new datasets for analysis. These simulated datasets allow for the estimation of the variability of the effect of interest

Patient-reported experience measures: questions asked to patients about the information they were given about their care, who was on their care team, how involved they were in their care, etc

Patient-reported outcome measures: questions asked to patients about their quality of life including questions about pain, fatigue, emotional functioning, etc

Prevalence: the fraction of the total population that has a specific characteristic or outcome

Prospective cohort: a type of study that enrolls a large number of people in a defined group and follows them over time

Standardization: a statistical method used to estimate the relationship between the variable of interest and the outcome of interest by comparing the population if everyone had the variable of interest to the population if no one has the variable of interest