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Quality of Life of Prostate Cancer Survivors Participating in a Remotely Delivered Web-Based Behavioral Intervention Pilot Randomized Trial

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Abstract

Background: Following a prostate cancer (PC) diagnosis, treatment-related symptoms may result in diminished quality of life (QoL). Improved diet and increased exercise may improve QoL in men with PC. **Methods:** We conducted a 4-arm pilot randomized trial to assess feasibility and acceptability of a 3-month web-based diet and exercise intervention, among men (>18 years of age) with PC (reported elsewhere). The purpose of this study is to describe the change in QoL measured by surveys (eg, QLQ-C30, PROMIS Fatigue) at enrollment and following the intervention. Men were randomized 1:1:1:1 to increasing levels of web-based behavioral support: Level 1: website; Level 2: Level 1 plus personalized diet and exercise prescription; Level 3: Levels 1-2 plus Fitbit and text messages; Level 4: Levels 1-3 plus 2 30-minute coaching calls. *T*-tests were used to compare pre-post change in mean QoL scores between each Level and Level 1. **Results:** Two hundred and two men consented and were randomized (n = 49, 51, 50, 52 for Levels 1-4, respectively). Men were predominantly white (93%), with a median age of 70 years (Intra-quartile Range [IQR]: 65,75) and 3 years (IQR: 1,9) post primary treatment for mostly localized disease (74% with T1-2). There were no meaningful changes in QoL, but there were notable trends. Level 3 participants had small improvements in QLQ-C30 Global Health (5.46; 95% CI: −0.02, 10.95) compared to Level 1. In contrast, Level 2 participants trended toward decreasing Global QoL (−2.31, 95% CI: −8.05, 3.42), which may reflect declines in function (eg, Cognitive: −6.94, 95% CI: −13.76, −0.13) and higher symptom burden (eg, Diarrhea: 4.63, 95% CI: −1.48, 10.74). **Conclusions:** This short, web-based intervention did not appear to have an impact on PC survivors' QoL. Most men were several years past treatment for localized disease; the potential for this approach to reduce symptoms and improve QoL in men who have worse health may still be warranted.

Keywords
cancer survivorship, diet, physical activity, exercise, patient-reported outcomes

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Background

There are more than 3.1 million prostate cancer survivors in the United States.[1] A prostate cancer diagnosis is most common in men aged 65 to 74 years and roughly 98% of those diagnosed will survive 10 years or more.[2] During this time, men may experience decreased quality of life (QoL) due to the combined effects of the cancer diagnosis, concurrent comorbidities, as well as aging and side effects of prostate cancer treatment, including incontinence, impotence, bowel dysfunction, fatigue, muscle loss, poor sleep quality,

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depression, isolation and loneliness, and increased frailty.[3-10] Prior research suggests treatment-related insults to QoL may subside in as little as 1 year after treatment, particularly for men undergoing radical prostatectomy.[11,12] It is less clear how long declines in physical, functional, emotional, and social well-being may last, especially considering they may be compounded by age-related declines.

An increasing body of evidence suggests that regular exercise, defined as 150 minutes per week of aerobic exercise and ≥2 sessions per week of strength training activity,[13] may improve prostate cancer clinical outcomes and QoL following diagnosis and treatment.[13-20] However, few men met these recommendations even when the evidence supporting them is strong. For example, in addition to reducing the risk of prostate cancer progression[17,20,21] and mortality,[17,20,22-26] participating in regular exercise, including aerobic and strength training activities, has been shown to offset age-related declines and relieve treatment side-effects, thereby improving prostate cancer survivors' QoL.[14-16] Yet, <25% of prostate cancer survivors meet aerobic exercise recommendations and only 4% meet those for resistance exercise.[27]

Evidence also suggests that changing certain dietary habits may improve disease-specific outcomes.[20,28-37] Further, prior reports have identified an association between healthy dietary patterns and higher levels or health-related QoL in the general population,[38] though less is known about the role of diet and QoL following a prostate cancer diagnosis. However, age-associated changes themselves, including declining muscle mass and changes in metabolism and physical functioning, can result in dietary shifts and ultimately decreased enjoyment of or interest in dietary intake.[39,40] In turn, poor nutrition among older adults has also been linked to decreased appetite and diminished capability in performing activities of daily living.[41]

Recognizing that a prostate cancer diagnosis may be a *teachable moment*—affording an opportunity to improve adherence to behavioral recommendations[42-45] —we conducted a pilot randomized trial to assess the feasibility and acceptability of a web-based intervention designed to support evidence-based dietary and exercise behaviors shown to improve prostate cancer-specific outcomes,[46] such as progression and disease-specific mortality.[20] Prior analyses showed the intervention to be feasible with no serious adverse effects and suggested it may modestly improve diet as well as exercise behaviors, particularly among men who were not meeting physical activity recommendations at baseline.[47] Additional data collected during the pilot study are relevant to understanding the impact of such technology-based approaches on other outcomes important to prostate cancer survivors. In this secondary analysis, we evaluate whether this practical and scalable technology-based intervention can also improve PC survivors' QoL.

Methods

Study Population

We conducted a multi-center 4-arm pilot randomized trial of a 3-month intervention among men (>18 years of age) with a self-reported diagnosis of prostate cancer (clinicaltrials.gov NCT03406013). There were no restrictions on stage of cancer or time since diagnosis. Men were identified through hospital cancer registry databases and from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry,[48] and mailed a letter and study brochure directing men to contact research staff to learn about the study. Study brochures were also placed in clinic waiting and exam rooms. To participate, men were required to speak English, have an email address, and have a personal device with internet and text messaging capability. All participants provided written consent and all study-related activities were done in accordance with and under the supervision of each study site's Institutional Review Board. Additional details have been reported elsewhere.[46]

Interventions

Men were block randomized 1:1:1:1 to increasing levels of web-based behavioral support. Participants randomized to **Level 1** received general educational information regarding exercise and diet, including a resource directory and study-specific guidelines posted on the study website. Participants randomized to **Level 2** received Level 1 resources plus personalized written diet and exercise recommendations, videos demonstrating recommended exercises, and a weekly e-log to track progress toward meeting recommendations. Participants randomized to **Level 3** received Level 1 to 2 resources plus text messages to support achieving diet and exercise recommendations (average: 4 texts/week, no response required) and a Fitbit Alta that integrated with the study website to display physical activity reports back to the participant. Participants randomized to **Level 4** received Level 1 to 3 resources plus access to two 30-minute coaching calls, 1 with an exercise trainer and 1 with a registered dietician. Participants were told they would be randomly assigned to receive access to websites with different tools and resources but were unaware of the resources they received relative to other participants. Additional details on randomization, interventions, and material content have been reported previously.[46]

Quality of Life Assessments

Patient-reported outcomes were assessed using both general population and cancer-specific validated questionnaires. All QoL assessments were obtained at study enrollment, at the end of intervention (3 months) and at 3-month follow-up after intervention ended (6 months).

QLQ-C30. The European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) is a cancer-specific 30-item questionnaire used to measure health-related QoL.[49] The QLQ-C30 includes 5 functioning scales (physical, role, cognitive, emotional, and social functioning), 3 symptom scales (fatigue, pain, nausea and vomiting), 6 symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global health status/QoL scale. Each scale's score ranges from 0 to 100 points; a higher score for global QoL and functioning reflect better health-related QoL or functioning, while a higher symptom scale score reflects higher symptom burden (eg, more severe pain). The QLQ-C30 scoring manual was used to calculate the scores.[50] Per scoring instructions, participants who responded to less than half of the scale components did not have a score calculated for that scale (ie, treated as missing; n = 57 for emotional functioning and financial difficulties subscales, n = 56 for all others). We used guidelines published in 2012 for interpreting longitudinal QoL score differences to quantify a meaningful change (see Table 4 in Cocks et al[51]), which expanded on the 1998 published guidelines.[52]

PROMIS fatigue. In addition to the fatigue symptoms assessed by the QLQ-C30, we used the Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue 8a – Adult v1.0 questionnaire to assess participants' fatigue.[53] Consistent with the PROMIS scoring manual, responses to all questions were summed and standardized using the T-Score Conversion Table.[54] The standardized score ranges from 33.1 to 77.8 (corresponding to a raw score of 8 to 40); a higher score is associated with greater symptoms of fatigue. We used the cancer calibration cohort within the HealthMeasures[55] Scoring Service (HM-SS) to impute responses for men who failed to answer at least one, but not all, PROMIS Fatigue questions. Men who failed to respond to at least 1 question were excluded from PROMIS analyses (n = 57). We followed the general threshold of a 5-point change to represent a minimally important difference, defined *a priori.*

PSQI. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) validated questionnaire.[56,57] The PSQI questionnaire evaluates 7 component scores (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, daytime dysfunction). Component scores range from 0 (no difficulty) to 3 (severe difficulty) and are summed to generate a Global PSQI Score ranging from 0 (no difficulty) to 21 (severe difficulty in all areas). Men were considered non-responders and were excluded from the PSQI analysis (n = 70) if they failed to respond to ≥1 of the questions. A global score <5 reflects good sleep quality.[56]

Statistical Analysis

Assessing QoL was a stated secondary objective of our pilot randomized trial.[46] Descriptive statistics of participants' socio-demographics, clinical characteristics, and randomization details are provided for each of the main QoL scores. We compared change in patient-reported QoL measures between enrollment and end of intervention for Levels 2, 3, and 4 compared to Level 1 via *t*-tests. Where differences were observed, we planned to report change in QoL measures between enrollment and 6 months to assess if effects were maintained after the intervention ended. Results are reported as mean change with 95% confidence intervals (CI). Paired *t*-tests were also used to compare the 3-month QoL measures to the baseline QoL measures within each level of intervention (see Supplemental Table 1).

As secondary trial endpoints, all QoL analyses were conducted among men with complete follow-up data. Though we report formal tests for change, our focus is on patterns of change, rather than statistical significance, consistent with guidelines for pilot trials.[58] All analyses were conducted in R version 3.6.3 using two-sided hypothesis testing and an alpha level of .05 to assess statistical significance.

Results

A total of 202 men with prostate cancer were consented and randomized to increasing levels of web-based behavioral support and provided access to the intervention: 49 assigned to Level 1, 51 to Level 2, 50 to Level 3, and 52 to Level 4. Of the 202 men randomized, 161 (80%) accessed their intervention (38 in Level 1, 38 in Level 2, 42 in Level 3, and 42 in Level 4); 35 of the 202 men (17%) were lost to follow-up at 3 months and an additional 11 (5%) were lost to follow-up at 6 months. Attrition was similar across levels. More details about study recruitment and retention were reported previously.[46,47]

Men were predominantly white (93%) and well-educated (83% with 4-year college degree or more). A total of 30 (15%) men reported receiving hormone therapy for the treatment of their prostate cancer. The overall median (IQR) age at enrollment was 70 (65-75) and was similar across all levels. However, by chance, men in Level 1 were farther out from their prostate cancer diagnosis compared to the group as a whole (median [IQR]: 9 years [4, 14] vs 4 years [2,10]). Table 1 shows median baseline QoL scores by participant characteristics. Men diagnosed with higher T-stage (T3-T4) reported lower median QLQ-C30 Global Health at baseline (75, IQR: 67, 83) compared to men diagnosed with stage

Table 1. Median Baseline QoL Scores by Sociodemographic and Clinical Characteristics of 202 Prostate Cancer Survivors Participating in A Technology-Supported Exercise and Dietary Intervention.

Characteristic	n (%)[a]	QLQ-C30 global health[b]	PROMIS fatigue[c]	PSQI[c]
All participants	202 (100)	83.3 (75.0, 91.7)	46.4 (41.0, 49.2)	5.0 (3.0, 7.0)
Age				
<65	56 (27.7)	83.3 (75.0, 91.7)	46.7 (42.6, 51.2)	6.0 (4.0, 8.0)
≥65	146 (72.3)	83.3 (75.0, 91.7)	46.4 (41.0, 49.0)	5.0 (3.0, 7.0)
Race				
White	187 (92.6)	83.3 (75.0, 91.7)	46.4 (41.0, 49.2)	5.0 (3.0, 7.0)
Other	13 (6.4)	83.3 (81.2, 85.4)	48.7 (44.0, 51.7)	8.0 (6.0, 8.5)
Education				
≤ High school	15 (7.4)	83.3 (83.3, 100.0)	47.7 (41.3, 48.7)	5.5 (4.0, 7.0)
2- or 4- year college	78 (38.6)	83.3 (75.0, 91.7)	46.4 (41.0, 51.2)	5.0 (3.0, 7.0)
Grad/prof degree	109 (54.0)	83.3 (75.0, 91.7)	46.4 (41.0, 48.7)	5.0 (3.0, 8.0)
PSA[d]				
≤10 ng/mL	129 (63.9)	83.3 (75.0, 91.7)	46.6 (41.2, 49.2)	5.0 (3.0, 8.0)
>10 ng/mL	48 (23.8)	83.3 (75.0, 91.7)	46.4 (40.9, 48.8)	5.0 (3.2, 7.0)
T-stage				
T1-T2	149 (73.8)	83.3 (75.0, 91.7)	45.4 (35.2, 48.7)	5.0 (3.0, 7.0)
T3-T4	40 (19.8)	75.0 (66.7, 83.3)	48.7 (46.7, 53.0)	6.0 (4.5, 8.5)
Gleason				
<7	38 (18.8)	83.3 (83.3, 97.9)	46.4 (41.3, 49.1)	6.0 (2.0, 7.0)
7	80 (39.6)	83.3 (66.7, 91.7)	46.4 (41.0, 48.7)	5.0 (3.0, 7.2)
>7	46 (22.8)	83.3 (66.7, 83.3)	46.7 (44.1, 50.1)	5.0 (4.0, 8.5)
ADT[e]	30 (14.9)	83.3 (75.0, 100)	44.1 (35.1, 49.5)	4.0 (3.0, 5.8)
Levels				
Level 1	49 (24.3)	83.3 (75.0, 95.8)	46.4 (44.0, 49.1)	5.0 (3.0, 7.0)
Level 2	51 (25.2)	83.3 (75.0, 91.7)	47.7 (41.4, 51.2)	5.0 (3.8, 8.0)
Level 3	50 (24.8)	83.3 (75.0, 91.7)	44.2 (36.5, 48.7)	5.0 (2.0, 7.0)
Level 4	52 (25.7)	83.3 (66.7, 91.7)	46.7 (38.2, 49.8)	5.0 (4.0, 7.0)

Abbreviations: ADT, androgen deprivation therapy; PROMIS, patient reported outcomes measurement system; PSA, prostate-specific antigen; PSQI, Pittsburgh sleep quality index; QLQ-C30, Quality of Life Questionnaire-Core 30; QoL, quality of life.

[a]Percentages may not sum 100% due to missingness: 2 men with unknown race, 25 men with unknown diagnostic PSA, 13 with unknown T-stage, 38 with unknown Gleason.

[b]Higher score reflects better QoL.

[c]Lower score reflects less fatigue/symptom burden.

[d]Median PSA value at diagnosis was 6.4 ng/mL.

[e]Reflects the number of men on active ADT treatment at enrollment. Two men reported active chemotherapy and 1 man reported active radiation therapy; counts were too low to summarize across scores.

T1-T2 (83, IQR: 75, 92), though scores were similar across other characteristics.

QLQ-C30

Mean changes in the QLQ-C30 are shown in Figure 1. Generally, most confidence intervals crossed 0 (ie, included the null), but there were notable trends. Compared to Level 1, men assigned to Level 2 tended to report worsening role, emotional, and cognitive functioning at 3 months, and increasing burden of fatigue, insomnia, diarrhea, and financial difficulties (Figure 1), resulting in a decreasing Global Health measure at 3 months (−2.31, 95% CI: −8.05, 3.42). Level 4 participants also reported a trend toward decreasing Global Health status compared to Level 1 (−1.52, 95% CI: −6.78, 3.74), though the only notable decline reported was an increase in financial difficulties. Conversely, there was a trend toward improving Global Health Status for men in Level 3 versus 1 (5.46, 95% CI: −0.02, 10.95), reflecting a small, but meaningful change.[51] Correspondingly, Level 3 reported improving emotional function and symptoms, including declining appetite loss, constipation, and diarrhea. The within-level mean change from baseline to 3-months is provided in Supplemental Table 1.

PROMIS Fatigue Score

Mean changes in PROMIS Fatigue scores are shown in Figure 2. Level 2 participants had increasing fatigue symptoms compared to Level 1 (3.24, 95% CI: 0.77, 5.71), with

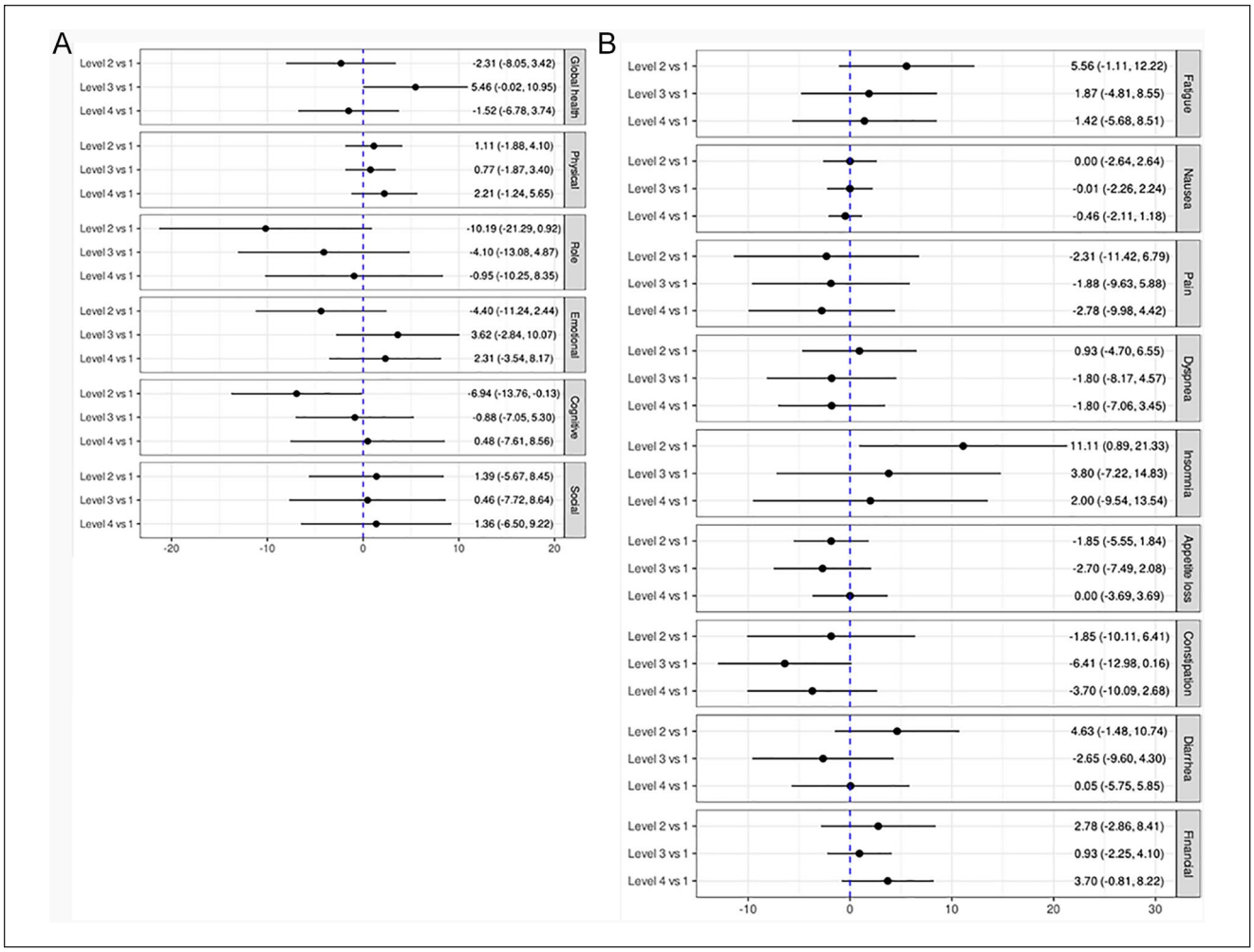

Figure 1. Mean change in QLQ-C30 sub-scales compared to level 1. (A) QLQ-C30 global health and function scales (a positive change score reflects better health/functioning comparing the level to the referent level). (B) QLQ-C30 symptoms scales and items (a negative change score reflects lower symptom burden comparing the level to the referent level).

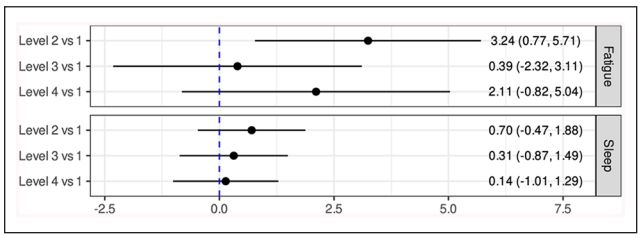

Figure 2. Mean change in PROMIS fatigue[a] and PSQI sleep index[b] scores compared to level 1.

[a]A positive change score is associated with greater fatigue comparing the level to the referent level.

[b]A positive change score is associated with worse sleep quality comparing the level to the referent level.

an upward trend also observed among Level 4 versus Level 1 participants (2.11, 95% CI: −0.82, 5.04). However, neither point estimate reached our *a priori* threshold of meaningful change (5 points). Level 3 participants did not demonstrate differences from men in Level 1 (0.39, 95% CI: −2.32, 3.11). The within-level mean change from baseline to 3-months is provided in Supplemental Table 1.

PSQI

Mean changes in PSQI scores are shown in Figure 2. There was essentially no change for men in Level 4 (0.14, 95% CI: −1.01, 1.29), Level 3 (0.31, 95% CI: −0.87, 1.49) or Level 2 (0.70, 95% CI: −0.47, 1.88) compared to Level 1 participants. The within-level mean change from baseline to 3-months is provided in Supplemental Table 1.

Given the lack of substantial change observed between baseline and 3 months, we did not analyze 6-month follow-up data.

Discussion

The primary aim of this pilot randomized trial was to assess the feasibility and acceptability of the web-based diet and exercise intervention. Findings from that analysis showed that the intervention was feasible and men were satisfied with the intervention, particularly those randomized to level 4. We also reported small improvements in diet and physical activity at 3 months for men randomized to level 4 versus level 1. Physical activity improvements were strongest among men who were insufficiently active at enrollment.[47] In this analysis of secondary outcomes, we observed little change in cancer-specific QoL outcomes among prostate cancer survivors participating in a pilot, 3-month, web-based intervention offering varying levels of educational information and behavioral support to improve diet and exercise behaviors. There may be several reasons for these results. First, it is possible that the intervention, though modestly effective at improving diet and exercise habits associated with improved prostate cancer outcomes,[47] may not improve QoL. Second, study participants were mostly diagnosed with localized prostate cancer. Prior studies have reported that QoL is notably better in men diagnosed with localized versus advanced disease.[59] Indeed, our lowest global QoL scores were observed among the 40 men diagnosed with T3-T4 disease and our baseline scores suggest that, overall, men had relatively high global QoL and functioning scores and low symptom burden. These high initial values could create a ceiling effect that may explain the limited influence of the intervention. A related reason may be that men in this study were a median of 3 years (IQR: 1, 9) out from their primary treatment for prostate cancer. There are both short- and long-term side effects associated with primary therapy, and these may differ in timing of effect, depending on type of therapy received.[6-9,60,61] Given this variability, it is also possible that clear patterns of change could not be observed, given our limited sample size and inability to examine participants based on these factors.

Some trends were observed within the 3 QoL metrics examined. Compared to Level 1, Level 2 participants demonstrated some decreases in QoL over the course of the intervention. There was also some evidence of a meaningful increase in QoL for Level 3 and a (nonmeaningful) decrease in QoL for Level 4 participants, though these trends were not consistent across all metrics. Given this lack of consistency and the possibility of chance findings due to multiple comparison, we caution against drawing conclusions from these noted trends. It is necessary to determine population-specific thresholds for meaningful clinical change. The EORTC[62] Quality of Life Group (QLG) supported the minimally important difference (MID) project whose aim was to establish MIDs for QLQ-C30 questionnaires according to cancer site.Notably, MID guidelines for prostate cancer have not yet been published, nor have MIDs been published for other scores within similar populations of prostate cancer survivors. Thus, general guidelines for meaningful change were used, as noted in the methods. However, previous literature suggest that these thresholds may vary by population and cancer type, in addition to QLQ-C30 subscale, and even the direction of change (ie, whether a positive score reflects better or worse QoL).[51,63-65] QLG MID project investigators have announced future plans to develop MIDs specific to prostate cancer, which may provide an opportunity to re-evaluate findings from this study. As a related example, although the change in PROMIS fatigue score did not reach the *a priori* threshold of meaningful change, Yost et al[66] noted a change score of 3 to 5 points using the 7-item PROMIS fatigue questionnaire in men with prostate cancer was a MID. A similar analysis to clarify MID for the 8-item PROMIS fatigue questionnaire used in this study may better inform these findings.

There are several limitations of this study to consider. The intervention was of limited duration and we did not select men with low baseline QoL scores. Men were diagnosed with different stages of disease, varied in their time since diagnosis, and were at varying points in their treatment pathway, all of which may influence QoL. We also acknowledge that men who self-select to participate in a lifestyle study may have better QoL than men who opt out. Further, the intervention was not specifically designed to improve QoL, nor powered to detect differences for this secondary outcome; any statistically significant results should be evaluated cautiously. Attrition may be more common among men experiencing increased symptom burden and decreased QoL. To the extent this is true, we may have missed a decline in QoL due to attrition, though rate of attrition was balanced across Levels. Lastly, individuals who volunteered were predominately white and highly educated which limits generalizability. Despite these potential shortcomings, given limited data on the impact of web-enhanced interventions to improve QoL in PC survivors, this report may be informative for future studies. Such studies may wish to consider a longer intervention period, inclusion of additional tools targeted at modifying specific QoL metrics (eg, meditation to reduce anxiety), and focus on men with worse disease severity or a greater burden of treatment.

Conclusion

This 3-month web-based intervention did not appear to have a meaningful impact on prostate cancer survivors' health-related QoL, sleep quality, or fatigue levels in the pilot sample. However, given the relative healthiness of the study population at enrollment, conclusions about the potential of this approach to reduce symptoms and improve QoL in men with more advanced disease or those more proximal to their primary treatment may still be warranted. Additionally, Black/African-American men bear a greater

burden of prostate cancer morbidity and mortality and are often under-represented in lifestyle intervention trials.[20,67,68] To address this, our team is conducting a qualitative assessment of preferences regarding diet and exercise resources for behavioral change, among non-white men with prostate cancer, to inform future tailored interventions. Overall, this pilot study suggests that in a population of more educated, white men with early-stage prostate cancer, more comprehensive (and/or longer) interventions may be needed to modify behavior to improve meaningfully QoL, sleep, and fatigue.

Authors' Note

Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SAK is associated with Fellow Health Inc. TMB is associated with AbbVie, Alliance Foundation Trials, Arvinas Inc, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Clovis Oncology, Corcept Therapeutics, Endocyte Inc, GlaxoSmithKline, Janssen Biotech, Janssen Japan, Janssen Research & Development, Medivation, Inc, Merck, OncoGenex, Pfizer, Salarius Pharmaceuticals, Sotio, Theraclone Sciences/OncoResponse. JMC's spouse is employed by GRAIL Inc. KP is employed by Movember. The authors are the developers/sponsors of the intervention evaluated in this report.

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Ethics Approval and Consent to Participate

All participants provided written consent, and all study-related activities were performed in accordance with and under the supervision of the institutional review board of each study site.

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Supplemental Material

Supplemental material for this article is available online.

Availability of Data and Materials

The datasets used during the current study may be available from the corresponding author on reasonable request.

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