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PHYSICAL ACTIVITY PATTERNS AND ASSOCIATIONS WITH HEALTH-RELATED QUALITY OF LIFE IN BLADDER CANCER SURVIVORS

Ajay Gopalakrishna, MHS¹, Thomas A. Longo, MD¹, Joseph J. Fantony, MD¹, Michael R. Harrison, MD², and Brant A. Inman, MD¹

¹Division of Urology, Duke University Medical Center, Durham, NC

²Division of Medical Oncology, Duke University Medical Center, Durham, NC

Abstract

Introduction—Physical activity has been shown to significantly improve health-related quality of life (HRQOL) and survivorship in a variety of cancer patients. However, little is known about the physical activity patterns of bladder cancer survivors and how these are related to HRQOL in the United States. Our objective was to describe self-reported physical activity patterns and HRQOL and examine the association between these measures in a large cohort of bladder cancer survivors.

Material and methods—In this cross-sectional study, long-term bladder cancer survivors identified through an institutional database were mailed a survey that included the Functional Assessment of Cancer Therapy Bladder Cancer (FACT-BL) and the International Physical Activity Questionnaire (IPAQ). Associations between HRQOL, as assessed by the FACT-BL, and physical activity, as assessed by the IPAQ, were examined by stratified analyses of HRQOL by different levels of physical activity, proportional odds ordinal logistic regression models, and local polynomial regression models.

Results—A total of 472 subjects (49% response rate) completed the survey. The mean age was 74 years; 81% were male and 87% were Caucasian. The median total weekly physical activity was 2794 MET-min. Subjects reporting “high” physical activity had a median FACT-BL score of 129, compared with 119 among those reporting “low” physical activity, a statistically and clinically significant difference. Similarly, subjects reporting “high” physical activity had a 2.2-fold increased odds of reporting higher global HRQOL, compared with subjects reporting “low” physical activity.

Conclusions—This large cohort of bladder cancer survivors reported high levels of physical activity. Physical activity was positively associated with HRQOL. Further studies investigating the

Corresponding author: Brant A. Inman, MD, MS, Box 103868, 3007 Snyderman Bldg., 905 La Salle Street, Durham, NC 27710, Asst: (919) 684-1322 Fax: (919) 668-7093, brant.inman@duke.edu.

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causal relationship between physical activity and HRQOL in the post-treatment setting in bladder cancer survivors are warranted.

Keywords

Bladder cancer; urothelial carcinoma; lifestyle factors; exercise; physical activity; quality of life

INTRODUCTION

Bladder cancer is the most common cancer affecting the urinary tract and the fourth leading cause of cancer death.[1] While bladder cancers are staged according to the TNM (tumor size, lymph node, and metastasis) system, two broad clinical phenotypes have been described: non-muscle invasive bladder cancer (NMIBC, T1) and muscle-invasive bladder cancer (MIBC, T2). NMIBC and MIBC have dramatically different prognoses and are consequently managed very differently.[2] NMIBC is characterized by a high local recurrence rate (ranging from 50–70%)[3] but a low risk of metastasis and death. The primary goal of NMIBC management is early detection and treatment of local recurrences in the bladder, which necessitates frequent follow-up visits and endoscopy, and consequently leads to significant healthcare costs and diminished patient health-related quality-of-life (HRQOL).[4] In MIBC, the main concerns are local progression of disease and distant metastasis, which consequently lead to more invasive forms of therapy such as removal of the bladder, bladder radiotherapy, and systemic chemotherapy. All of these treatments for MIBC carry significant risk of treatment-related loss of HRQOL.[5]

Physical activity is a general health intervention that is inexpensive, relatively low-risk, has numerous health benefits, and increases HRQOL. It is unknown whether the physical activity habits of bladder cancer survivors affect their HRQOL. The objectives of this study were to (a) describe the physical activity patterns of a large cohort of bladder cancer survivors, and (b) determine if physical activity in these bladder cancer survivors was associated with their HRQOL.

METHODS

Inclusion/Exclusion criteria

After IRB approval, subjects were identified using the Duke Enterprise Data Unified Content Explorer (DEDUCE) tool, which merges multiple clinical data sources into a searchable dataset. Inclusion criteria were age ≥ 18 years, histologically-confirmed diagnosis of bladder cancer, and a history of receiving some aspect of their cancer care at Duke University Medical Center from 1/1/1996 onwards. Subjects were excluded if deceased or at high risk of being deceased (e.g., hospice care, metastases and last follow-up >2 years prior), unable to read and/or understand English (for questionnaire validity), no medical visit at our institution within 2 years, and known diminished mental capacity. After screening, eligible subjects were sent a composite survey by mail querying their HRQOL and physical activity level. Completed surveys (or a study withdrawal card) were returned in self-addressed envelopes and abstracted into an electronic database. A reminder postcard was sent 4 weeks after the initial mailing to non-respondents.

FACT-BL—The HRQOL of subjects was assessed using a Functional Assessment of Cancer Therapy (FACT) questionnaire, a validated set of questions designed to measure HRQOL of patients treated for chronic illnesses (particularly cancer).[6] The FACT-BL is comprised of 5 subscales: physical well-being (PWB, 7 items), emotional well-being (EWB, 6 items), social well-being (SWB, 7 items), functional well-being (FWB, 7 items), and additional concerns (13 items). The additional concerns scale evaluates urinary function (2 items), sexual function (2 items), bowel function (2 items), weight loss (2 items), body image (1 item), and concerns about the ostomy appliance (2 items). There are 3 composite scores: (1) overall FACT-BL (sum of all subscales), (2) FACT-G (sum of PWB, EWB, SWB, and FWB subscales), and (3) the Trial Outcome Index (TOI, sum of the PWB, FWB, and additional concerns subscales). Higher values indicate better HRQOL. The minimum clinically important difference (MCID) values have not been established for the FACT-BL. Therefore, we estimated these values based on other FACT surveys as follows:[7–10] 2–3 points for FACT-BL subscales, 3–7 points for FACT-G, 4–6 points for TOI, and 6–8 points for the FACT-BL total score.

IPAQ-L—Physical activity was measured using the 27-item International Physical Activity Questionnaire Long form (IPAQ-L), a validated tool designed to quantify physical activity. [11, 12] It asks about physical activities performed for 10 min during the previous week. Respondents report time spent in physical activity performed at work, during leisure time, domestic activities, and transport. The physical activity is then mapped to metabolic equivalents values (METs) using one of three intensities: “vigorous” (8.0 METs), “moderate” (4.0 METs), and “walking” (3.3 METs). Total weekly physical activity is estimated by weighting the time spent in each activity by its corresponding MET energy expenditure, and subjects are categorized into “low” (not meeting criteria for “moderate” or “high”), “moderate” (3 days/week of vigorous-intensity activity of 20 min/day OR 5 days of moderate-intensity activity and/or walking of 30 min/day, OR 5 days/week of any activity achieving a total physical activity of 600 MET-min/week), or “high” (3 days/week of vigorous-intensity activity achieving 1500 MET-min/week OR 7 days of any activity achieving 3000 MET-min/week).[13]

Statistical analysis

Continuous variables with normal distributions were summarized with means, continuous variables with non-normal distributions with medians, and categorical variables with counts and percentages. To address unit non-response and item non-response, we conducted a comprehensive missing data analysis. To determine if unit non-response was affected by clinico-demographic variables, we compared key clinical covariates between respondents and non-respondents. Then, variables marginally associated with non-response univariately ($p < 0.15$) were entered into a multivariable logistic regression model with questionnaire response as the binary outcome. Item non-response was addressed first by looking for missingness patterns using aggregation plots, matrix plots, and recursive partitioning.[14, 15] Using the MICE algorithm, multiple imputation was used to generate 50 complete datasets.[15] The imputation model included key variables associated with missingness as well as variables judged useful for imputation by the MICE algorithm using influx and outflux statistics.[16] Because HRQOL scores were non-normally distributed and could not

be easily transformed to normality, stratified analyses were conducted using quantile regression models (with $\tau = 0.5$) and the standard error calculated using the xy-pair bootstrap-based method.[17] HRQOL scores were divided into quartiles and proportional odds ordinal logistic regression models were used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for associations between HRQOL and physical activity. These analyses were repeated to control for relevant covariates,[18] including age, gender, race, BMI, American Joint Committee on Cancer (AJCC) stage, comorbidities, and procedure type (radical cystectomy or transurethral resection). To visualize associations between physical activity and HRQOL, we used locally weighted scatterplot smoothing (lowess) curves, which employ local polynomial regression, a nonparametric method that uses weighted least squares regression in a k-nearest-neighbor-based model.[19] Regression models were fit to each of the 50 datasets and model parameters were pooled using Rubin's rules.[20] All analyses were done using R 3.2.3, with packages FACTScorer, mice, rpart, polr, and quantreg installed.[15, 17, 21]

RESULTS

Of 1057 mailed questionnaires, there were 472 respondents (had completed at least 1 question). The flow of subjects is shown graphically in Supplemental Figure 1 and key characteristics of respondents and non-respondents summarized in Table 1. Multivariable modeling showed that non-respondents were more likely to be younger, female, African American, current smokers, have less recent surgeries, and a more advanced disease stage (Supplemental Table 1). Of respondents, 257 (54%) had complete information on all variables. The average fraction of missingness across all variables was 9.6% and the highest fraction of missingness was noted for total physical activity (30.9%) from the IPAQ-L.

Summary measures of lifestyle behaviors

Table 2 shows physical activity patterns as measured by the IPAQ-L. Median amount of physical activity in the "Work" domain was 0, indicating that over half of the respondents were retired. The highest amount of physical activity was in the "Domestic" domain. Total median physical activity performed was approximately 2800 MET-min/week.

Associations between lifestyle behaviors and HRQOL

Overall HRQOL and HRQOL stratified by physical activity level are shown in Table 3. This analysis shows that physical well being, functional well being, additional concerns, FACT-G, trial outcome index, and FACT-BL all increased with increasing physical activity level. Notably, social and emotional well being did not improve with increasing physical activity.

The odds of better HRQOL scores at higher physical activity levels are shown in Table 4. In univariate analyses, the odds of a better HRQOL was not significantly different between low and moderate physical activity. However, relative to low or moderate physical activity level, subjects with a high physical activity level had an increased odds ratio of better HRQOL across all composite scales. After adjusting for potential confounders, including age, gender, race, smoking status, comorbidities, AJCC stage, and procedure type, the results were mildly attenuated but remained significant.

A local polynomial regression (loess) model of the association between physical activity and global HRQOL is shown in Figure 1. Consistent with other analyses, there is a significant positive association between HRQOL and physical activity.

DISCUSSION

Our study examined HRQOL and physical activity in a large cohort of bladder cancer survivors. HRQOL scores were moderately favorable, with higher scores in physical and social well being subscales than emotional and functional well being. When compared with the general US population,[22] our cohort had higher scores across social well being, functional well being, and FACT-G scales and similar scores in physical and emotional well being scales. This unexpected finding suggests that long-term bladder cancer survivors tend to have a comparable quality of life to the general American population. The caveat to this finding, however, is that the vast majority in our cohort had stage 0–2 disease and been treated with TURBT. The results may have been different if a larger proportion of our cohort had more advanced disease.

Respondents reported a median of 2794 MET-min/week of total physical activity and over 75% reported “moderate” or “high” physical activity. A global survey of 18–65 year old adults using the IPAQ-L found that the median reported physical activity was 3699 MET-min/week, significantly higher than our cohort.[11] To control for geography, we examined physical activity data from the 2009 Behavioral Risk Factor Surveillance System (BRFSS) survey of North Carolina participants. Only 46% of North Carolina adults reported the equivalent of “moderate” or “high” physical activity.[23] Although the questions used in the BRFSS differ from that of the IPAQ, it is evident that our cohort of bladder cancer survivors report higher levels of physical activity than North Carolina participants of the BRFSS study. It is possible that bladder cancer survivors truly participate in higher levels of physical activity as a result of oncologists’ counseling about American Cancer Society recommendations, which suggest that patients aim for at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity per week.[24] However, it is also possible that our cohort over reported their physical activity. Our clinical experience performing cardiopulmonary stress testing in bladder cancer patients has demonstrated substantially impaired VO₂ max values (a key measure of physical fitness), so we were expecting far lower physical activity levels than we observed. Previous studies have shown that the IPAQ may overestimate actual physical activity performed.[25] Additionally, it is possible that respondents were more physically active than non-respondents.

An interesting finding was that the highest amount of physical activity was in the “domestic” domain. This may be in part due to the survey being conducted during the summer months in a region with a relatively moderate climate. Many studies that examine physical activity measure only leisurely physical activity.[18, 26] Our results suggest that it is important to incorporate global physical activity, as leisurely physical activity alone may not always offer an accurate estimate of overall physical activity level.

The positive association between physical activity and HRQOL was consistent with our hypothesis and findings in other studies in bladder cancer survivors. Blanchard *et al.* and

Karvinen *et al.* have both examined associations between leisurely exercise and HRQOL in bladder cancer survivors and found a positive association.[18, 27] A recent systematic review on associations between lifestyle factors and HRQOL in bladder cancer survivors reinforced our results.[28] These findings are also consistent with those in multiple other cancers, including colon, prostate, ovarian, and endometrial cancers.[29–33] Mechanisms through which physical activity improves HRQOL may include improved aerobic fitness, increased strength, decreased anxiety and depression, and improved body image.[34] The benefits of physical activity in bladder cancer survivors reach beyond improvement in HRQOL. A meta-analysis by Keimling *et al.* showed that physical activity is associated with a decreased risk of bladder cancer.[35] While that study examined risk for new diagnoses of bladder cancer, it is plausible that risk for recurrence may also be lower.

Limitations

The cross-sectional nature of our study was a limitation as we were unable to assess changes in HRQOL and physical activity from pre- to post-treatment. We are also unable to infer any causal relationships between physical activity and HRQOL. The findings are primarily applicable to long-term survivors. We cannot draw conclusions as to implications for short-term HRQOL outcomes. Additionally, lifestyle behaviors were evaluated by self-reporting, and respondents may have under- or over-reported data, affecting the associations between HRQOL and physical activity. Lastly, missing data in incomplete questionnaires was a limitation, though minimized through multiple imputation.

CONCLUSIONS

This large cohort of bladder cancer survivors reported high levels of physical activity. Physical activity level was positively associated with HRQOL. Further studies investigating the causal relationship between lifestyle factors and HRQOL in bladder cancer survivors are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Bladder cancer survivors report high levels of physical activity
- The highest amount of physical activity came from domestic activities
- Increasing physical activity was associated with increasing quality of life
- Exercise could represent an easy method of improving quality of life

Figure 1.

Table 1

Comparison of respondents and non-respondents

	Respondents (N=472)	Non-respondents (N=490)	P-value ^I
Age , mean (sd)	73.9 (9.9)	71.5 (12.4)	0.001
Gender			
Male	382 (81%)	334 (68%)	<0.001
Female	90 (19%)	156 (32%)	
Race			
Caucasian	412 (87%)	388 (79%)	0.003
African American	36 (8%)	58 (12%)	
Other	24 (5%)	44 (9%)	
BMI , mean (sd)	27.9 (5.5)	28.2 (6.0)	0.398
Elixhauser score , mean (sd)	3.37 (1.7)	3.52 (1.9)	0.192
Smoking status			
Current	38 (8%)	80 (17%)	<0.001
Former	317 (68%)	272 (56%)	
Never	113 (24%)	131 (27%)	
Procedure type			
Radical cystectomy	130 (28%)	127 (26%)	0.219
Partial cystectomy	13 (3%)	7 (2%)	
Transurethral resection	325 (69%)	347 (72%)	
Laser ablation	2 (0.4%)	0 (0%)	
Procedure year , median (IQR)	2012 (2009, 2013.5)	2012 (2006, 2014)	0.056
Cancer type			
Urothelial carcinoma	458 (98%)	463 (97%)	0.339
Other	11 (2%)	17 (4%)	
AJCC stage group			
0	307 (71%)	290 (67%)	0.081
1	56 (13%)	45 (10%)	
2	34 (8%)	56 (13%)	
3	17 (4%)	24 (6%)	
4	17 (4%)	16 (4%)	
Grade			
Low	153 (38%)	173 (43%)	0.197
High	248 (62%)	232 (57%)	

^I Welch's *t*-test used for continuous variables, except procedure year where Wilcoxon's rank-sum test is used, and Fisher's exact test used for categorical variables.

Table 2

Physical activity patterns of bladder cancer survivors as determined by IPAQ-L

Physical activity component	Median [95% CI] MET-min/week
Work	0 [0–0]
Transportation	196 [129–262]
Domestic and yard work	868 [630–1106]
Leisure time	323 [212–435]
Total physical activity	2794 [2226–3363]
Physical activity level	
Low	24%
Medium	26%
High	50%

Table 3

Health-related quality of life of bladder cancer survivors, stratified by physical activity level.

	Range	MCID	Overall HRQOL Median [95%CI]	Physical activity level			P-value ^I
				Low Median [95%CI]	Moderate Median [95%CI]	High Median [95%CI]	
FACT subscales							
Physical well being	0–28	2–3	25.1 [24.4–25.8]	24.1 [22.9–25.3]	25 [24.1–25.8]	26 [25.5–26.5]	0.002
Functional well being	0–28	2–3	22 [21.1–22.9]	18.6 [16.5–20.8]	19.9 [18.3–21.4]	23.6 [22.3–24.9]	<0.001
Social well being	0–28	2–3	24 [23.6–24.4]	23.3 [21.8–24.9]	22.3 [20.9–23.8]	24 [23.5–24.5]	0.054
Emotional well being	0–24	2–3	20.9 [20.2–21.6]	20 [19.1–20.9]	20.8 [19.6–22]	21 [20.6–21.4]	0.244
Additional concerns	0–48	2–3	34.8 [34–35.6]	33.4 [31.7–35.1]	34.3 [32.6–36]	36 [34.9–37.1]	0.025
FACT composite scores							
FACT-G (general)	0–108	3–7	90 [88.3–91.7]	85.3 [80.1–90.5]	86.7 [83.2–90.3]	93.9 [91.8–96]	<0.001
Trial outcome index	0–104	4–6	81.2 [79.5–83]	76.2 [72.3–80]	77.9 [74.5–81.3]	85.1 [82.9–87.3]	<0.001
FACT-BL	0–156	6–8	124.7 [122.7–126.8]	118.8 [113.4–124.3]	120.6 [115.6–125.5]	129.3 [126.5–132.0]	<0.001

^IWald P-value for change in HRQOL by physical activity level. MCID: Minimum clinically important difference

Table 4

Odds of higher health-related quality of life among different physical activity levels

	Low-Moderate ¹		Low-High ²		Moderate-High ³	
	Unadjusted OR [95%CI]	Adjusted ⁴ OR [95%CI]	Unadjusted OR [95%CI]	Adjusted ⁴ OR [95%CI]	Unadjusted OR [95%CI]	Adjusted ⁴ OR [95%CI]
FACT-G (general)	1.16 [0.67, 2.00]	0.93 [0.52, 1.64]	2.67 [1.66, 4.30]	2.46 [1.47, 4.11]	2.17 [1.37, 3.44]	2.54 [1.57, 4.10]
Trial outcome index	1.56 [0.91, 2.66]	1.20 [0.69, 2.08]	2.89 [1.79, 4.68]	2.52 [1.51, 4.18]	1.78 [1.19, 2.67]	2.03 [1.33, 3.09]
FACT-BL	1.21 [0.71, 2.08]	0.93 [0.53, 1.65]	2.52 [1.56, 4.06]	2.22 [1.33, 3.72]	1.95 [1.27, 3.01]	2.27 [1.45, 3.55]

¹ Odds ratio for higher health related quality of life in "Moderate" physical activity relative to "Low"² Odds ratio for higher health related quality of life in "High" physical activity relative to "Low"³ Odds ratio for higher health related quality of life in "High" physical activity relative to "Moderate"⁴ Adjusted for age, gender, race, smoking status, AJCC stage, comorbidities, and procedure type