



European Association of Urology



Diet and Exercise Are not Associated with Skeletal Muscle Mass and Sarcopenia in Patients with Bladder Cancer

Yingqi Wang^a, Andrew Chang^a, Wei Phin Tan^a, Joseph J. Fantony^a, Ajay Gopalakrishna^a, Gregory J. Barton^a, Paul E. Wischmeyer^b, Rajan T. Gupta^c, Brant A. Inman^{a,*}

^a Division of Urology, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA; ^b Department of Anesthesiology, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA; ^c Department of Radiology, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA

Article info

Article history:

Accepted April 29, 2019

Associate Editor:

Ashish Kamat

Keywords:

Sarcopenia
Bladder cancer
Physical activity
Diet
Lifestyle

Abstract

Background: There is limited understanding about why sarcopenia is happening in bladder cancer, and which modifiable and nonmodifiable patient-level factors affect its occurrence.

Objective: The objective is to determine the extent to which nonmodifiable risk factors, modifiable lifestyle risk factors, or cancer-related factors are determining body composition changes and sarcopenia in bladder cancer survivors.

Design, setting, and participants: Patients above 18 yr of age with a histologically confirmed diagnosis of bladder cancer and a history of receiving care at Duke University Medical Center between January 1, 1996 and June 30, 2017 were included in this study.

Outcome measurements and statistical analysis: Bladder cancer survivors from our institution were assessed for their dietary intake patterns utilizing the Diet History Questionnaire II (DHQ-II) and physical activity utilizing the International Physical Activity Questionnaire long form (IPAQ-L) tools. Healthy Eating Index 2010 (HEI2010) scores were calculated from DHQ-II results. Body composition was evaluated using Slice-O-Matic computed tomography scan image analysis at L3 level and the skeletal muscle index (SMI) calculated by three independent raters.

Results and limitations: A total of 285 patients were evaluated in the study, and the intraclass correlation for smooth muscle area was 0.97 (95% confidence interval: 0.94–0.98) between raters. The proportions of patients who met the definition of sarcopenia were 72% for men and 55% of women. Univariate linear regression analysis demonstrated that older age, male gender, and black race were highly significant predictors of SMI, whereas tumor stage and grade, chemotherapy, and surgical procedures were not predictors of SMI. Multivariate linear regression analysis demonstrated that modifiable lifestyle factors, including total physical activity ($p = 0.830$), strenuousness (high, moderate, and low) of physical activity ($p = 0.874$), individual nutritional components (daily calories, $p = 0.739$; fat, $p = 0.259$; carbohydrates, $p = 0.983$; and protein, $p = 0.341$), and HEI2010 diet quality ($p = 0.822$) were not associated with SMI.

* Corresponding author. Duke University Medical Center, 3007 Snyderman Bldg, 905 La Salle Street, Durham, NC 27710, USA. Tel.: +1 919 684 1322; Fax: +1 919 668 7093.
E-mail address: brant.inman@duke.edu (B.A. Inman).



Conclusions: Lifestyle factors including diet quality and physical activity are not associated with SMI and therefore appear to have limited impact on sarcopenia. Sarcopenia may largely be affected by nonmodifiable risk factors.

Patient summary: In this report, we aim to determine whether lifestyle factors such as diet and physical activity were the primary drivers of body composition changes and sarcopenia in bladder cancer survivors. We found that lifestyle factors including dietary habits, individual nutritional components, and physical activity do not demonstrate an association with skeletal muscle mass, and therefore may have limited impact on sarcopenia.

© 2019 European Association of Urology. Published by Elsevier B.V. All rights reserved.

1. Introduction

For oncologists, understanding why some patients with cancer do well while others do poorly is an essential goal. In many cancers, malnutrition is an important risk factor that is associated with poorer overall and cancer-specific survival [1]. In fact, 10–20% of cancer-related deaths are thought to be related primarily to malnutrition rather than the malignancy itself [1]. The etiology of malnutrition is often multifactorial and includes loss of appetite (due to either biological and psychosocial factors related to the cancer, or its treatment), competitive consumption of nutritional resources by tumors, and cancer-induced systemic inflammatory responses that alter metabolism [2,3].

A prolonged state of malnutrition ultimately leads to progressive loss of skeletal muscle (SM) mass and can develop into a condition known as sarcopenia [1,4]. The most common method used to quantify SM mass is the skeletal mass index (SMI), which is a validated and gender-specific reproducible tool [5]. The SMI uses a single cross-sectional computed tomography (CT) scan performed at the L3 vertebral level to measure body composition into adipose tissue and SM compartments [5,6].

Even though sarcopenia is thought of as a malnourished state, it can also occur in conjunction with obesity [6]. Patients with bladder cancer (BC) and sarcopenia have a higher incidence of chemotherapy-related toxicity, poorer surgical outcomes, and reduced overall survival [6–8]. Sarcopenia is thought to be multifactorial and have been attributed to immobility, malnutrition, changes in hormones and metabolism, systemic inflammation, and neuromuscular aging [9]. However, there is a very limited understanding about why sarcopenia is happening in BC, and which modifiable and nonmodifiable patient-level factors affect its occurrence. The objective of the current study is to determine the extent to which nonmodifiable risk factors (eg, age, gender, and race), modifiable lifestyle risk factors (eg, diet and physical activity), or cancer-related factors (eg, tumor stage) are determining SM mass and sarcopenia in BC survivors.

2. Patients and methods

2.1. Participants

After Institution Review Board approval, we used the Duke Enterprise Data Unified Content Explorer (DEDUCE) tool to identify participants for

this study [10,11]. Briefly, we included patients above 18 yr of age with a histologically confirmed diagnosis of BC and a history of receiving care at Duke University Medical Center between January 1, 1996 and June 30, 2017. Patients were excluded if they were deceased or at a high risk of dying (eg, hospice care, metastases, and last follow-up >2 yr before), were unable to read and/or understand English (for questionnaire validity), had no medical visit at our institution within 2 yr, or had a diagnosis associated with diminished mental capacity (eg dementia). Eligible individuals were contacted and administered a detailed cross-sectional survey (details below). Demographics, smoking status, body mass index (BMI), comorbidities, and cancer-related details were abstracted from patients' electronic medical records, and comorbidities were quantified with the Elixhauser index [12]. All patients provided informed consent to participate in the study.

2.2. Physical activity and diet assessment

Physical activity was measured via International Physical Activity Questionnaire long form (IPAQ-L), which is a 27-item validated tool designed to quantify physical activity [10,11]. Respondents report time spent in physical activity performed at work and during leisure time, domestic activities, and transport. The physical activity is then mapped to metabolic equivalents (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 individuals are categorized into groups with "low" (not meeting the criteria for "moderate" or "high"), "moderate" (≥ 3 d/wk of vigorous-intensity activity of ≥ 20 min/d, or ≥ 5 d of moderate-intensity activity and/or walking of ≥ 30 min/d, or ≥ 5 d/wk of any activity achieving total physical activity of \geq MET-min/wk), or "high" (≥ 3 d/wk of vigorous-intensity activity achieving ≥ 1500 MET-min/wk or 7 d of any activity achieving ≥ 3000 MET-min/wk) physical activity.

Diet was quantified using the Diet History Questionnaire II (DHQ-II), which is a validated food frequency questionnaire involving 151 questions covering portion size of over 134 food items and eight supplements [13,14]. It uses food frequency methodology (usual consumption frequency and portion size over the past month) and diet history methodology (assessment of cooking methods and staple foods). The Healthy Eating Index 2010 (HEI2010) score is a validated and reliable single quantitative measure of diet quality and is calculable from the DHQ-II [15,16]. The components were scored for a maximum of 100 points (higher scores reflect a better-quality diet). According to the United States Department of Agriculture, an HEI2010 score of < 51 is categorized as "poor," 51–80 represents "needing improvement," and > 80 represents "good" [17].

2.3. Body composition analysis

Axial images from CT scans were converted into the Digital Imaging and Communications in Medicine (DICOM) format for analysis. Two axial

images at the L3 vertebral level were collected per patient: the first image was obtained when both transverse processes of L3 were visible, while the second image was the image immediately inferior to the first (usually 5 mm inferior). Slice-O-Matic software (version 5.0; TomoVision, Montreal, Quebec, Canada) was used to perform body composition analysis into the SM area, subcutaneous and intramuscular adipose tissue (SAT) area, and visceral adipose tissue (VAT) area, measured in mm² [18]. CT Hounsfield unit thresholds ranged from –29 to 150 for SM, –190 to –30 for SAT, and –150 to –50 for VAT. Values for each component were averaged over the two axial images. The skeletal muscle index (SMI), subcutaneous adipose tissue index (SATI), and visceral adipose tissue index (VATI) were calculated by dividing the component areas by height (m²) and reported as cm²/m². Sarcopenia is defined as an SMI of ≤ 52.4 cm²/m² for men or ≤ 38.5 cm²/m² for women [6], excess subcutaneous adipose tissue as a SATI of ≥ 50 cm²/m² for men or ≥ 42 cm²/m² for women [19], and excess VAT as a VATI of ≥ 52.9 cm²/m² for men or ≥ 51.5 cm²/m² for women [19]. Two raters (one medical student and one urology resident) were trained to read Slice-O-Matic images by an expert genitourinary radiologist, and each was randomly assigned to read half of the images. To allow for interrater reliability measurement, both raters and the expert radiologist read an overlap of 30 cases independently, selected by random number generation.

2.4. Statistical analysis

We assessed several variables as potential predictors of body composition using univariate linear regression. Nonmodifiable demographic factors included age (yr), sex, race (Caucasian and African American), estimated annual income (US dollars), and comorbidity load (Elixhauser index). Modifiable lifestyle risk factors included smoking status (yes, no, and previous), dietary composition, and physical activity. Cancer-related factors included cancer stage (American Joint Committee on Cancer stage groups 0–4), tumor grade (low and high), type of most recent surgical procedure (transurethral resection of bladder tumor, partial cystectomy, or radical cystectomy), time from procedure to current assessment (yr), number of tumor occurrences, and chemotherapy use.

Medians and their interquartile ranges (IQRs) were used to summarize continuous variables, while categorical variables were summarized with counts and percentages. Diet*Calc version 1.5.0 software was used to analyze the DHQ-II questionnaire [15], and HEI2010 scores were calculated using SAS version 9.2 (SAS Institute, Cary, NC, USA). To assess interrater reliability with the Slice-O-Matic software, we measured the intraclass correlation coefficient (ICC) and created Bland-Altman plots for each rater pairing. Prior to the study, a power calculation was performed for 90% power and alpha of 5%, and estimating that a 30-individual overlap would be sufficient to measure the ICC. To address missing data from item nonresponse of the surveys, we constructed a multiple imputation model as previously described [10]. Briefly, we generated 20 complete datasets, and generalized linear regression models were fit to each of the 20 imputed dataset and pooled using Rubin's rules. Identical models were fit to the complete case data for comparison. We performed exploratory univariate analyses on demographic factors (gender, age, race and socioeconomic status), comorbidity (Elixhauser comorbidity index and smoking status), cancer-related factors (tumor stage, tumor grade, and use of chemotherapy), dietary factors (caloric intake and HEI), and IPAQ-L. Multivariate analysis was then performed based on statistically significant findings in the univariate analysis. R 3.5.1 for Rstudio 1.1.456 was used for statistical analyses, with the key packages (mice, rpart, dplyr, psych, and VIM) installed [20].

3. Results

A total of 459 of 952 (48% response rate) responded to the questionnaire. Only 285 of 952 patients (30%) underwent CT

Table 1 – Clinical characteristics of the study cohort

Patient characteristics (N = 285)		
Age (yr)	73.8	(68.3, 80.2)
Male	227	79.6%
Race		
White	251	88.1%
Black	25	8.8%
Other	9	3.2%
Elixhauser comorbidity score	3	(2, 5)
Smoking status		
Current	22	7.7%
Former	196	68.7%
Never	67	23.5%
BMI	27.3	(24.3, 31.0)
Median income (ZIP code)	\$48 994	(\$40 024, \$60 659)
Tumor characteristics		
AJCC stage group		
0	161	56.5%
1	41	14.4%
2	29	10.2%
3	16	5.6%
4	3	1.1%
Missing	35	12.2%
Grade		
Low	78	27.3%
High	172	60.4%
Missing	35	12.2%
Procedure characteristics		
Procedure type		
TURBT	182	63.8%
Partial cystectomy	7	2.5%
Radical cystectomy	96	33.6%
Time since procedure (yr)	2.3	(1.0, 4.9)

AJCC = American Joint Committee on Cancer, BMI = body mass index; TURBT = transurethral resection of bladder tumor. Ranges for age, Elixhauser comorbidity score, BMI, and income represent interquartile range.

of the abdomen and pelvis, with a median time of 6 mo between imaging and survey completion, and were included in the study. Characteristics of the patient cohort are shown in Table 1. (Supplementary Fig. 2) The majority of patients (80%) were male with a median age of 73.8 yr (IQR 68.3–80.2). The stage distribution favored non-muscle-invasive tumors over muscle-invasive tumors in a manner consistent with known disease distribution, and only 34% of patients had previously been treated by cystectomy. A total of 72% of men and 55% of women met the gender-specific criterion for sarcopenia.

Interrater reliability with the Slice-O-Matic software was very high for all body composition components studied. The ICC was highest for the SM area at 0.97 (95% confidence interval [CI]: 0.94–0.98), followed by VAT area at 0.96 (95% CI: 0.93–0.98) and SAT area at 0.94 (95% CI: 0.89–0.97). Bland-Altman plots (Supplementary Fig. 1) showed no major patterns of disagreement between independent rater pairs for any of the three measurements, confirming that Slice-O-Matic can be used reproducibly by raters of different levels of medical experience, ranging from medical students to expert radiologists. Body composition measurements for SM, visceral fat, and subcutaneous fat are shown in Table 2. The results from the self-reported physical activity level (IPAQ-L) and diet quality (DHQ-II) are also shown in Table 2. The median physical activity level was 2616 MET-min/wk. Total physical activity level was not

Table 2 – Body composition, physical activity, and diet

Body composition measurements		
Skeletal muscle		
Cross sectional area (cm ²)	139.9 ^a	(112.5, 162.9) ^b
Index (cm ² /m ²)	45.6 ^a	(38.2, 52.1) ^b
Sarcopenia present, males	161	71%
Sarcopenia present, females	32	55%
Visceral adipose tissue		
Cross sectional area (cm ²)	211.6 ^a	(130.1, 299.3) ^b
Index (cm ² /m ²)	72.2 ^a	(44.2, 94.7) ^b
Excess, males	162	71%
Excess, females	25	43%
Subcutaneous adipose tissue		
Cross sectional area (cm ²)	198.0 ^a	(141.6, 281.4) ^b
Index (cm ² /m ²)	65.4 ^a	(46.1, 89.8) ^b
Excess, males	155	68%
Excess, females	46	79%
Self-reported physical activity (IPAQ-L)		
Total (MET-min/wk)	2616 ^a	(658, 5864) ^b
Activity level		
Low	53	18%
Moderate	51	18%
High	96	33%
Missing	87	30%
Self-reported diet quality (DHQ2)		
Carbohydrate (g/d)		
Total	200.0 ^a	(147.1, 267.4) ^b
Sugars	91.3 ^a	(63.7, 132.0) ^b
Fat (g/d)		
Total	64.4 ^a	(46.5, 86.9) ^b
Saturated	19.7 ^a	(14.1, 28.0) ^b
Monounsaturated	23.9 ^a	(17.3, 32.4) ^b
Polyunsaturated	13.9 ^a	(9.8, 18.6) ^b
Protein (g/d)	63.8 ^a	(46.9, 84.9) ^b
Calories (kcal/d)	1632 ^a	(1254, 2170) ^b
Healthy Eating Index 2010		
Total score	66.3 ^a	(59.0, 72.2) ^b
Good	20	7%
Needs improvement	227	80%
Poor	29	10%
Missing	9	3%
DHQ2 = Diet History Questionnaire II; IPAQ-L = International Physical Activity Questionnaire long form; MET = metabolic equivalent.		
^a Median.		
^b Interquartile range.		

calculated in 30% of patients due to incomplete responses. A total of 48% of patients reported a high level of physical activity, based on the IPAQ-L questionnaire.

Univariate linear regression analysis demonstrated that age (median −0.3 IQR [−0.4, −0.2]), male gender (9.5 [6.8, 12.2]), and black race (5.3 [1.2, 9.5]) were predictors of SMI, whereas male gender (26.7 [16.3, 37.0]), black race (−22.3 [−38.5, −8.1]), and Elixhauser comorbidity score (5.6 [3.1, 8.2]) were predictors of VATI. Age (−0.8 [−1.3, −0.3]), male gender (−24.5 [−35.6, −13.5]), and Elixhauser comorbidity score (8.2 [5.6, 10.9]) were also predictors of SATI (Table 3). However, on univariate linear regression analysis, we found that socioeconomic status, Elixhauser comorbidity index, smoking status, tumor stage and grade, chemotherapy, and surgical procedures were not predictors of SMI.

Multivariate linear regression analysis (adjusted for age, gender, and race) demonstrated that modifiable lifestyle factors, including total physical activity ($p = 0.830$),

strenuousness (high, moderate, and low) of physical activity ($p = 0.874$), individual nutritional components (daily calories, $p = 0.739$; fat, $p = 0.259$; carbohydrates, $p = 0.983$; protein, $p = 0.341$), and overall diet quality as measured by HEI2010 ($p = 0.822$) were not associated with SMI (Table 4). However, an increase in physical activity was associated with lower VATI ($p = 0.025$) and lower SATI ($p = 0.011$). Similarly, a “good” HEI2010 score was strongly associated with lower VATI ($p < 0.001$) and lower SATI ($p = 0.001$) when compared with “poor” or “needs improvement” diets.

The relationships between physical activity quantity in MET-min/wk (Fig. 1) and diet quality measured by the HEI2010 score (Fig. 2) and body composition are shown graphically. These figures visually demonstrate the contributions of physical activity and diet relative to a patient’s age, gender, and race to overall body composition. These data demonstrate that the factors most strongly determining body composition are nonmodifiable.

4. Discussion

Sarcopenia has strongly been associated with all-cause mortality in patients with BC [8,21]. However, there is a very limited understanding about the etiology of sarcopenia in BC, and which modifiable and nonmodifiable patient-level factors are associated with its occurrence. In this study, we report on patient-related factors associated with body composition in patients with BC, including nonmodifiable demographic factors, modifiable lifestyle factors, and cancer-related factors. Our study shows that modifiable lifestyle factors, such as physical activity and dietary habits, did not appear to be associated with body composition. Rather, nonmodifiable factors (age, gender, and race) were associated with body composition. This data therefore raise important questions as to how best to address sarcopenia, as defined by a reduced SMI. This data suggest that routine dietary habits and physical activity are not associated with sarcopenia in patients with BC.

Additionally, we found a negative correlation between physical activity and adipose tissue quantity (SAT and VAT) in patients with BC. This relationship is logical given that an increase in physical activity result in increased energy expenditure and a decrease in body fat. Since obesity as determined by BMI is associated with worse oncological outcomes in patients with BC, this finding suggests that physical activity may be an important modifiable factor to reduce obesity and improve outcomes in patients with BC [22]. This may support the rationale of preoperative nutritional and physical activity optimization in patients, for example.

Interestingly, there are conflicting data pertaining to sarcopenia and higher T staging in the literature [21,23]. In our study, we did not find any association between higher T staging and SMI. We believe that this is because previous studies dichotomize SMI, which we did not. We intentionally decided to measure SMI as a continuous variable, as this is less prone to cut-point-dependent findings.

Table 3 – Predictors of body composition by univariate linear regression

	Skeletal muscle index	Visceral adipose tissue index	Subcutaneous adipose tissue index
Age	–0.3 (–0.4, –0.2)	–0.1 (–0.6, 0.4)	–0.8 (–1.3, –0.3)
Male gender	9.5 (6.8, 12.2)	26.7 (16.3, 37.0)	–24.5 (–35.6, –13.5)
Race			
White	Ref	Ref	Ref
Black	5.3 (1.2, 9.5)	–23.3 (–38.5, –8.1)	5.6 (–10.6, 21.8)
Other	2.0 (–4.7, 8.6)	–9.0 (–33.6, 15.6)	–10.6 (–36.8, 15.7)
Elixhauser comorbidity	0.2 (–0.5, 1.0)	5.6 (3.1, 8.2)	8.2 (5.6, 10.9)
Smoking status			
Current	Ref	Ref	Ref
Former	1.6 (–6.1, 2.8)	2.5 (–14.0, 19.1)	6.5 (–10.9, 23.8)
Never	–3.9 (–8.8, 1.0)	0.6 (–17.5, 18.6)	10.2 (–8.8, 29.2)
Median income (ZIP code)	4.8e–5 (–1.3e–5, 1.1e–4)	2.2e–5 (–2.1e–4, 2.5e–4)	–1.2e–5 (–2.5e–4, 2.3e–4)
AJCC stage group			
0	Ref	Ref	Ref
1	–4.3 (–11.6, 3.1)	–20.0 (–47.3, 7.2)	6.5 (–21.4, 34.4)
2	0.2 (–6.3, 6.7)	–13.1 (–37.2, 11.1)	6.0 (–18.7, 30.7)
3	4.2 (–0.8, 9.3)	–1.0 (–19.8, 17.8)	2.7 (–16.5, 22.0)
4	–1.6 (–5.6, 2.4)	–6.3 (–21.2, 8.6)	–15.9 (–31.2, –0.7)
Grade			
Low	Ref	Ref	Ref
High	0.1 (–1.8, 2.0)	–1.5 (–8.4, 5.4)	2.9 (–4.2, 10.1)
Procedure type			
TURBT	Ref	Ref	Ref
Partial cystectomy	4.5 (–3.1, 12.2)	10.1 (–18.1, 38.2)	18.1 (–11.6, 47.9)
Radical cystectomy	–0.3 (–2.8, 2.2)	–8.4 (–17.6, 0.9)	1.0 (–8.7, 10.8)
Total physical activity	0 (–0.0003, 3e–04)	–0.0016 (–0.0028, –5e–04)	–0.0015 (–0.0026, –3e–04)
Physical activity category			
High	Ref	Ref	Ref
Moderate	2.6 (–0.8, 6.0)	18.4 (6.0, 30.8)	21.4 (9.0, 33.7)
Low	0.8 (–2.5, 4.2)	15.1 (2.8, 27.4)	7.4 (–4.7, 19.6)
Calories (kcal/d)	0.001 (0.000, 0.002)	0.003 (–0.002, 0.009)	0.002 (–0.003, 0.008)
Fat (g/d)	0.032 (0.002, 0.063)	0.158 (0.043, 0.273)	0.111 (–0.012, 0.234)
Carbohydrates (g/d)	0.003 (–0.007, 0.014)	–0.001 (–0.041, 0.038)	0.009 (–0.033, 0.051)
Protein (g/d)	0.033 (0.001, 0.066)	0.110 (–0.011, 0.232)	0.047 (–0.082, 0.177)
HEI2010: total score	–0.1 (–0.2, 0.0)	–0.5 (–0.9, –0.1)	–0.3 (–0.7, 0.2)
HEI2010: diet quality			
Good	Ref	Ref	Ref
Needs improvement	2.1 (–2.4, 6.6)	22.3 (5.4, 39.1)	14.6 (–3.3, 32.6)
Poor	2.8 (–2.9, 8.4)	28.6 (7.6, 49.6)	24.2 (1.8, 46.6)

AJCC = American Joint Committee on Cancer; HEI = Healthy Eating Index; Ref = reference; TURBT = transurethral resection of bladder tumor; Data is presented by Linear regression coefficient with its 95% confidence interval. Bold indicate statistical significance

Table 4 – Predictors of body composition by multivariate linear regression

	Skeletal muscle index ^a		Visceral adipose tissue index ^a		Subcutaneous adipose tissue index ^a	
	Est	p value	Est	p value	Est	p value
Total physical activity	–2.92e–05	0.830	–1.02e–3	0.025	–1.47e–3	0.011
Physical activity category		0.874		0.001		<0.001
High	Ref		Ref		Ref	
Moderate	0.81		13.37		19.71	
Low	0.12		17.11		12.96	
Calories (kcal/d)	2.24e–4	0.739	5.04e–4	0.851	0.0028	0.320
Fat (g/d)	0.018	0.259	0.092	0.125	0.122	0.049
Carbohydrates (g/d)	–1.04e–4	0.983	–0.015	0.443	0.010	0.611
Protein (g/d)	0.016	0.341	0.023	0.721	0.066	0.308
HEI2010: total score	0.014	0.799	–0.40	0.053	–0.231	0.280
HEI2010: diet quality		0.822		<0.001		0.025
Good	Ref		Ref		Ref	
Needs improvement	1.19		22.02		15.67	
Poor	0.95		29.68		21.23	

Est = estimate, HEI = Healthy Eating Index; Ref = reference.

^a Adjusted for age, gender, and race. Bold indicate statistical significance

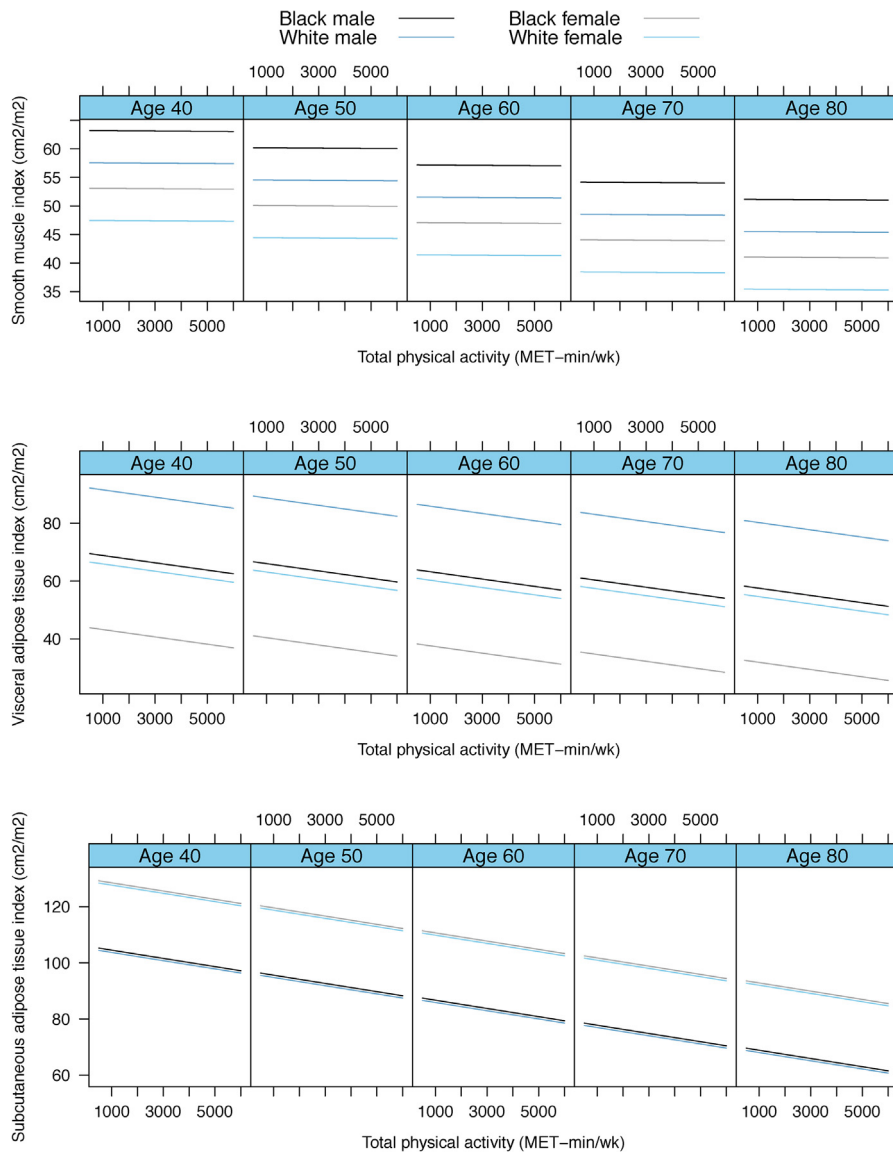


Fig. 1 – SMI, VATI, and SATI based on total physical activity, age, race, and gender. MET = metabolic equivalent; SATI = subcutaneous adipose tissue index; SMI = skeletal muscle index; VATI = visceral adipose tissue index.

Even though there have been no data evaluating the correlation between physical activity and muscle mass in patients with BC, limited data have been reported to show a correlation between increasing muscle mass and an increase in aerobic and resistance exercise in patients with leukemia and breast cancer [24]. Surprisingly in this study, we found that physical activity does not seem to correlate with SM mass. Possible explanations for our finding include the fact that the IPAQ-L is a measure of total physical activity, but does not quantify aerobic and resistance exercise directly. Second, muscle mass may not be representative of muscle strength and endurance. Last, genetics play an important role in the determination of muscle mass [25], as clearly demonstrated by differences in sex and race. We found that SM decreases with age and is higher in black males, followed by white males, black females, and white females, across all age groups (Fig. 1).

However, visceral fat decreases with age and is highest in white males, followed by black males, white females, and black females. Subcutaneous fat was highest in white females, followed by black females, white males, and black males (Fig. 1). These findings concur with the published literature, suggesting that genetic variation has an influence on SM traits and that there may be different clinically meaningful thresholds of muscle mass for which function is impaired [25]. Based on our study, age, race, and gender are strong determinants of SM mass and must be accounted for when interventions are planned. As CT scan determined sarcopenia is not the standard of care in most centers, these data may help guide early preoperative identification of patients at risk for sarcopenia, and guide targeted surgical prehabilitation nutrition and exercise efforts [26,27] to improve muscle mass reserve. This is a key area that demands further research and clinical trials.

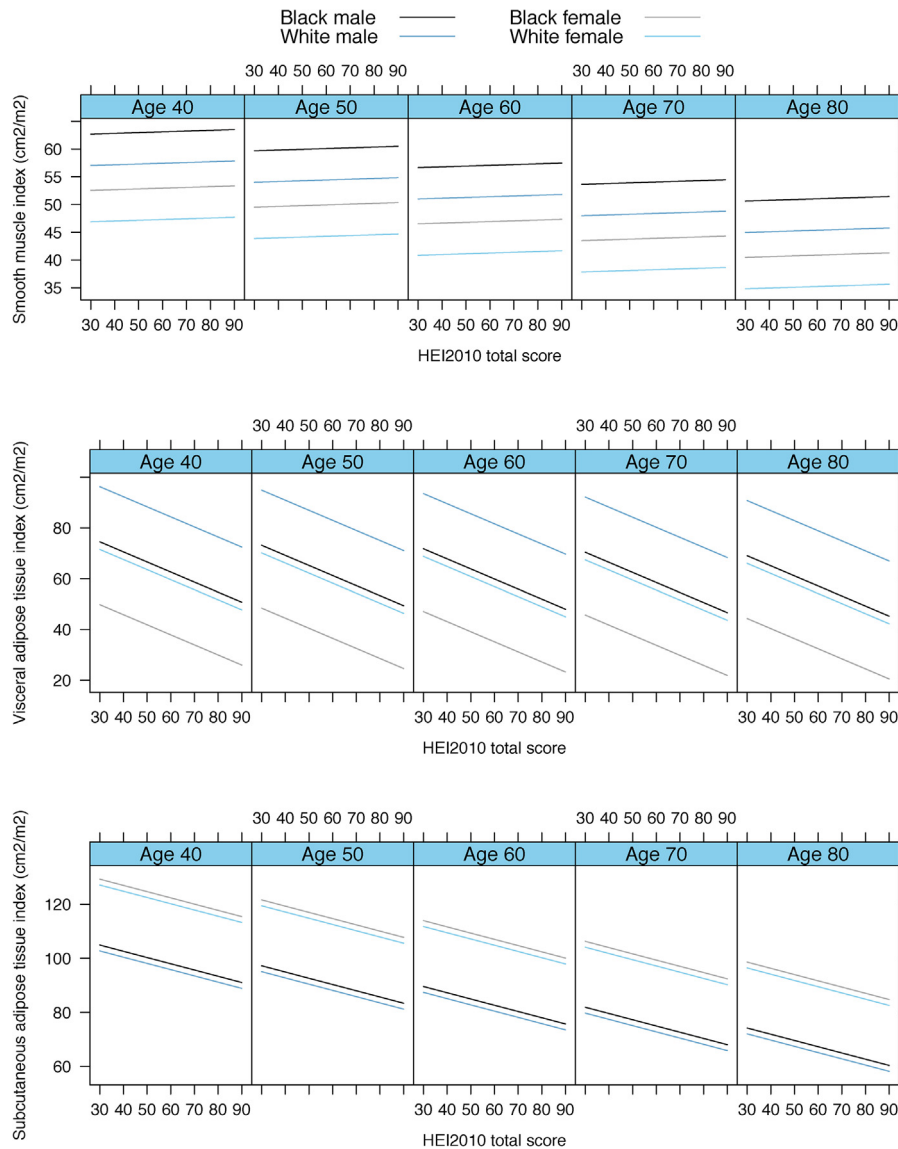


Fig. 2 – SMI, VATI, and SATI based on Healthy Eating Index, age, race, and gender. HEI = Healthy Eating Index; SATI = subcutaneous adipose tissue index; SMI = skeletal muscle index; VATI = visceral adipose tissue index.

There are multiple limitations to our study. The cross-sectional nature of this study does not imply causal relationships between risk factors and body composition. This study does not determine whether further muscle wasting can be prevented with structured and targeted physical activity and nutritional interventions, and in fact, recent clinical trials suggest that improving body composition may be possible [28]. The findings of this study are primarily applicable to long-term survivors. Another limitation of our study was that the diet was evaluated by detailed self-reporting, which is subjected to recall bias, and it is possible that respondents may have under- or over-reported frequencies or quantities of foods consumed and physical activity performed, which may have affected the estimates of diet composition and quality. The total caloric intake was also lower than anticipated in our study,

although the dietary patterns in our cohort were similar to those of the age-matched general US population and prior cancer survivorship studies [29]. Data for physical activity was also not available in 30% of patients given the questionnaires were returned incomplete, even though 100% of patients in this series completed the questionnaire. Given that the median time from imaging to survey completion was 6 mo, body composition of each individual may not be representative of the actual result at the time of survey, even though we showed that time from imaging to survey was not a predictor of SMI. Our study cohort consisted of only 8% African Americans and 21% female patients, but this is over-representative of the US population with BC since African Americans and females represent, respectively, 5% and 24% of cases captured in the Surveillance, Epidemiology, and End Results Program [30]. Despite

these limitations, we present a very large comprehensive study to assess diet quality, dietary patterns, and SM and adipose tissue mass in patients with BC.

5. Conclusions

In this cohort of BC survivors, we show that the lifestyle factors including diet quality and physical activity do not appear to be associated with SM mass, and therefore routine changes in diet and physical activity may have limited impact on sarcopenia. Sarcopenia is associated with worse outcomes in BC patients and appears to be caused by nonmodifiable risk factors. Early preoperative identification of patients with these risk factors may help identify BC patients at high risk for sarcopenia, and guide structured surgical prehabilitation efforts and research to improve muscle mass reserve. Further research is warranted to determine the extent that structured physical activity and nutritional intervention protocols modify the sarcopenic state in patients with BC.

Author contributions: Brant A. Inman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Inman.

Acquisition of data: Wang, Chang, Gopalakrishna, Fantony, Gupta.

Analysis and interpretation of data: Chang, Tan, Inman.

Drafting of the manuscript: Tan.

Critical revision of the manuscript for important intellectual content: Inman, Wischmeyer, Gupta, Barton.

Statistical analysis: Inman, Chang.

Obtaining funding: Inman.

Administrative, technical, or material support: Barton, Tan, Wischmeyer.

Supervision: Inman, Gupta.

Other: None.

Financial disclosures: Brant A. Inman certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Wei Phin Tan is supported by the Ruth L. Kirschstein NRSA Institutional Research Training Grant (T32 CA093245).

Funding/Support and role of the sponsor: This work was supported by the National Cancer Institute (NCI).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.euo.2019.04.012](https://doi.org/10.1016/j.euo.2019.04.012).

References

- [1] Arends J, Baracos V, Bertz H, et al. ESPEN Expert Group recommendations for action against cancer-related malnutrition. *Clin Nutr* 2017;36:1187–96.
- [2] Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr* 2017;36:49–64.
- [3] Pressoir M, Desné S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in French comprehensive cancer centres. *Br J Cancer* 2010;102:966.
- [4] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;39:412–23.
- [5] Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008;33:997–1006.
- [6] Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008;9:629–35.
- [7] Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: current concepts and imaging implications. *Am J Roentgenol* 2015;205:W255–66.
- [8] Baracos V, Kazemi-Bajestani SMR. Clinical outcomes related to muscle mass in humans with cancer and catabolic illnesses. *Int J Biochem Cell Biol* 2013;45:2302–8.
- [9] Ogawa S, Yakabe M, Akishita M. Age-related sarcopenia and its pathophysiological bases. *Inflamm Regen* 2016;36:17.
- [10] Gopalakrishna A, Chang A, Longo TA, et al. Dietary patterns and health-related quality of life in bladder cancer survivors. *Urol Oncol* 2018;36:469.e21–e.
- [11] Gopalakrishna A, Longo TA, Fantony JJ, Harrison MR, Inman BA. Physical activity patterns and associations with health-related quality of life in bladder cancer survivors. *Urol Oncol* 2017;35:540.e1–e.
- [12] Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.
- [13] Thompson FE, Subar AF, Brown CC, et al. Cognitive research enhances accuracy of food frequency questionnaire reports: results of an experimental validation study. *J Am Diet Assoc* 2002;102:212–25.
- [14] Subar AF, Thompson FE, Kipnis V, et al. Comparative validation of the Block Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. *Am J Epidemiol* 2001;154:1089–99.
- [15] Kantoff P, Higano CS. Integration of immunotherapy into the management of advanced prostate cancer. *Urol Oncol* 2012;30:S41–7.
- [16] National Institutes of Health. Diet History Questionnaire, version 2.0. Applied Research Program, National Cancer Institute; 2010.
- [17] Center for Nutrition Policy Promotion. The Healthy Eating Index. 1995.
- [18] Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. *Annu Rev Nutr* 1997;17:527–58.
- [19] Ebadi M, Martin L, Ghosh S, et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. *Br J Cancer* 2017;117:148–55.
- [20] RStudio Team. RStudio: integrated development for R. Boston, MA: RStudio Inc.; 2015.
- [21] Psutka SP, Carrasco A, Schmit GD, et al. Sarcopenia in patients with bladder cancer undergoing radical cystectomy: impact on cancer-specific and all-cause mortality. *Cancer* 2014;120:2910–8.
- [22] Zhao L, Tian X, Duan X, Ye Y, Sun M, Huang J. Association of body mass index with bladder cancer risk: a dose–response meta-analysis of prospective cohort studies. *Oncotarget* 2017;8:33990–4000.
- [23] Mayr R, Fritsche HM, Zeman F, et al. Sarcopenia predicts 90-day mortality and postoperative complications after radical cystectomy for bladder cancer. *World J Urol* 2018;36:1201–7.

- [24] Stene GB, Helbostad JL, Balstad TR, Riphagen II, Kaasa S, Oldervoll LM. Effect of physical exercise on muscle mass and strength in cancer patients during treatment – a systematic review. *Crit Rev Oncol Hematol* 2013;88:573–93.
- [25] Roth SM. Genetic aspects of skeletal muscle strength and mass with relevance to sarcopenia. *Bonekey Rep* 2012;1:58.
- [26] Whittle J, Wischmeyer PE, Grocott MPW, Miller TE. Surgical prehabilitation: nutrition and exercise. *Anesthesiol Clin* 2018;36:567–80.
- [27] Wischmeyer PE, Carli F, Evans DC, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus statement on nutrition screening and therapy within a surgical enhanced recovery pathway. *Anesth Analg* 2018;126:1883–95.
- [28] Ritch CR, Cookson MS, Clark PE, et al. Perioperative oral nutrition supplementation reduces prevalence of sarcopenia following radical cystectomy: results of a prospective randomized controlled trial. *J Urol* 2019;201:470–7.
- [29] Zhang FF, Liu S, John EM, Must A, Demark-Wahnefried W. Diet quality of cancer survivors and noncancer individuals: results from a national survey. *Cancer* 2015;121:4212–21.
- [30] Wang Y, Chang Q, Li Y. Racial differences in urinary bladder cancer in the United States. *Sci Rep* 2018;8:1252.