Proceedings of the Nutrition Society (2018), **77**, 382–387 doi:10.1017/S0029665118000423
 First published online 4 June 2018

The Nutrition Society Winter Conference was held at the Royal Society of Medicine, London on 5–6 December 2017

Conference on 'Diet, nutrition and the changing face of cancer survivorship' Symposium 1: Nutrition during diagnosis and treatment

Clinical implications of low skeletal muscle mass in early-stage breast and colorectal cancer

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Although obesity has now been widely accepted to be an important risk factor for cancer survival, the associations between BMI and cancer mortality have not been consistently linear. Although morbid obesity has clearly been associated with worse survival, some studies have suggested a U-shaped association with no adverse association with overweight or lower levels of obesity. This 'obesity paradox' may be due to the fact that BMI likely incompletely captures key measures of body composition, including distribution of skeletal muscle and adipose tissue. Fat and lean body mass can be measured using clinically acquired computed tomography scans. Many of the earlier studies focused on patients with metastatic cancer. However, skeletal muscle loss in the metastatic setting may reflect end-stage disease processes. Therefore, this article focuses on the clinical implication of low skeletal muscle mass in early-stage non-metastatic breast and colorectal cancer where measures of body composition have been shown to be strong predictors of disease-free survival and overall survival and also chemotherapy toxicity and operative risk.

Breast cancer: Colorectal cancer: Sarcopenia

Although obesity has now been widely accepted to be an important risk factor for cancer survival[1], the associations between BMI and cancer mortality have not been consistently linear. Although morbid obesity (>35 kg/m^2) has clearly been associated with worse survival, some studies have suggested a U-shaped association with no adverse association with normal/overweight, but worse outcomes with both underweight and higher levels of obesity. This 'obesity paradox' may be due to the fact that BMI likely incompletely captures key measures of body composition, including distribution of skeletal muscle and adipose tissue[2]. Fat and lean body mass can be measured in a variety of ways, including bioelectrical impedance electrical analysis, dual-energy X-ray absorptiometry, MRI and computed tomography (CT) scans. With the exception of CT scans, most of the other types of scans are not routinely done on patients in the clinical setting. Conversely, clinically acquired CT scans can be used to estimate both the muscle and adipose tissue compartments with high accuracy and are often done for staging or planning purposes at diagnosis and surveillance for a variety of early-stage cancers, facilitating the incorporation of assessment of body composition into routine clinical care[3]. Skeletal muscle mass can be precisely estimated from single-slice axial CT images at the third lumbar vertebra (L3)[4]. It should be noted that the cut-points used to define sarcopenia (or low muscle mass) have varied considerably across studies, making cross-study comparisons difficult at times[3]. Many of the earlier studies focused on patients with metastatic cancer where serial CT scans are readily available. However, skeletal muscle loss in the metastatic setting may reflect end-stage disease processes that may not be generalisable to the non-metastatic setting and may not be easily reversible. Therefore, this paper will focus on the clinical

Abbreviations: CT, computed tomography; HR, hazard ratio; SMI, skeletal muscle index.

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implication of low skeletal muscle mass in early-stage non-metastatic breast and colorectal cancer where there may still be actionable findings and potential insights into mechanisms.

Potential mechanisms relating body composition and survival

While the precise mechanisms linking skeletal muscle to survival after a cancer diagnosis are not established, it is likely that skeletal muscle operates through physiologic and metabolic (e.g. inflammation) as well as behavioural (e.g. reduced physical activity due to de-conditioning and fatigue) pathways. Skeletal muscle has local autocrine, paracrine and endocrine effects, but also secretes cytokines and other myokines (including IL-6, IL-8, IL-15 and leukaemia inhibitory factor) leading to systemic effects[5]. Therefore, higher levels of muscle may decrease the impact of obesity-induced inflammation[6], whereas lower levels of muscle could lead to local and systemic inflammation[7]. Several studies suggest that systemic inflammation may lead to ongoing muscle loss in cancer patients and in part drive the associations with cancer survival[8,9]. *In vitro* studies also highlight the key role of inflammation. For example, exercise-induced myokines released from skeletal muscle, such as IL-6, suppress tumour growth[10]. Loss of muscle may also disrupt oxidative pathways, encouraging tumour growth[11]. Muscle is also an important target of insulin-mediated glucose uptake and low muscle mass may be associated with insulin resistance[12,13]. Finally, the low skeletal muscle may influence survival after a cancer diagnosis by its impact on other crucial cancer outcomes such as surgical complications and treatment-related toxicity leading to chemotherapy dose modifications or interruptions, which will be discussed in the following sections.

Colorectal cancer

Colorectal cancer is the second leading cause of cancer death both in the UK[14] and in the USA[15]. The search for modifiable risk factors to improve the rates of recurrence and survival is, therefore, a public health priority. Overwhelmingly, the focus in early-stage colorectal cancer has been on excess adiposity with less attention to another major component of body composition: skeletal muscle mass. However, accumulating evidence suggests that low skeletal muscle mass at colorectal cancer diagnosis, often referred to as sarcopenia or myopenia, is highly prevalent and associated with cancer recurrence, survival, surgical complications and treatment-related toxicities. Studies using this technique included heterogeneous patient populations and variable cut-points to define 'low' skeletal muscle mass, leading to a wide range of prevalence estimates (from 17[16] to 60 %[17]) for sarcopenia.

Association with cancer recurrence and survival

Multiple studies evaluate the association of low skeletal muscle mass at colorectal cancer diagnosis with overall and recurrence-free survival[2,5,18–20]. Fewer have examined colorectal cancer-specific survival in non-metastatic patients[2]. One meta-analysis combined the results of three small studies, two of which were in metastatic colorectal cancer patients, and reported that low skeletal muscle at colorectal cancer diagnosis was associated with a more than 2-fold risk of overall mortality (hazard ratio (HR) = 2·25; 95 % CI 1·63, 3·09)[18]. The largest non-metastatic cohort study published to date included 3262 stage I–III colorectal patients diagnosed 2006–2011 and reported that patients with sarcopenia at diagnosis were at increased risk of both overall mortality (HR = 1·27; 95 % CI 1·09, 1·48) and colorectal cancer-specific mortality (HR = 1·46; 95 % CI 1·19, 1·79). This study utilised optimal stratification to determine BMI and sex-specific cut-points for sarcopenia (normal/overweight men <52·3 and women <38·6 cm^2/m^2 and obese men <54·3 and women <46·6 cm^2/m^2)[2]. While heterogeneity in study design and patient population complicates the interpretation of this body of evidence and precludes a comprehensive meta-analysis, most studies report a statistically significant increased mortality for patients with low skeletal muscle mass[2,5,18–20]. To our knowledge, no study reports a protective association of low skeletal muscle mass.

Association with complications after colorectal cancer surgery

Several authors have reviewed the research on the associations between body composition and adverse cancer outcomes besides survival in colorectal cancer[19–22]. In colorectal cancer specifically, multiple studies report a higher risk of complications[19–23], short-term mortality after surgery[19–22] and the need for postoperative rehabilitation[23]. The largest of these studies was by Malietzas *et al.* who reviewed 805 patients (90 % stage I–III) undergoing elective colorectal cancer surgery resection and found that myopenic obesity was associated with a higher 30 d rate of major complications (22 *v.* 13 %, $P = 0{\cdot}019$) and mortality ($P > 0{\cdot}001$)[19]. Lieffers *et al.* also noted that sarcopenia was an independent predictor of higher rates of infection (OR = 4·6; 95 % CI 1·5, 13·9) and need for inpatient rehabilitation (OR = 3·1, 95 % CI 1·04, 9·4) among 234 colorectal cancer patients undergoing resection[23]. Similarly, studies have also reported longer hospital stays for patients with low skeletal muscle[16,19,23]. It should be noted that all of these analyses controlled for BMI and that body composition measures generally outperformed BMI in predicting the risk of complications. In sum, the data from the colorectal cancer literature strongly suggest that assessments of body composition and skeletal muscle from CT scans could significantly impact preoperative risk assessment and improve decision-making around a selection of candidates for surgery and post-operative treatment[23,24].

https://doi.org/10.1017/S0029665118000423 Published online by Cambridge University Press

Associations with treatment-related toxicities

Another important pathway through which low muscle could influence colorectal cancer survival is by reducing the efficacy of life-saving cancer therapies. Low muscle has been associated with treatment toxicities, dose reductions and early discontinuation of chemotherapy, all of which potentially compromise the effectiveness of adjuvant therapies which are being administered with curative intent[24]. Most chemotherapies are dosed based on body surface area (m^2), for which the recommended mg per m^2 are derived from clinical trials assessing dose-limiting toxicities along with efficacy. Yet, many patients still experience severe toxicity and are subsequently dose-reduced, or treatment may be delayed or discontinued early. Multiple studies have shown that non-metastatic colorectal cancer patients with lower skeletal muscle consistently experience higher rates of grade 3/4 toxicity, such as neutropenia, diarrhoea, neuropathy and hand–foot syndrome[25–29]. Furthermore, another study found that among 533 non-metastatic colon cancer patients receiving FOLFOX chemotherapy, those in the lowest tertile of muscle mass were more likely to be dose-reduced (OR = 2·28; 95 % CI 1·19, 4·36), dose-delayed (OR = 2·24; 95 % CI 1·37, 3·66) and to discontinue chemotherapy prematurely (OR = 2·34; 95 % CI 1·04, 5·24), than those in the highest tertile[30].

A possible explanation is that lower muscle may result in a smaller tissue volume for distribution of certain cancer therapies, with potentially lower capacity for metabolism and clearance of drugs, thereby leading to greater toxicity. Additionally, body surface area dosing does not account for variation in muscularity, which has been hypothesised to influence the pharmacokinetics of chemotherapy[31]. To our knowledge, only one study to date has examined the pharmacokinetics of 5-fluorouracil in patients receiving FOLFOX for colorectal cancer chemotherapy; the authors found no significant differences in first cycle 5-fluorouracil area-under-the-concentration–time curve, though patients with a higher dose per kilogram lean body mass experienced greater toxicity[32]. Ongoing trials (Clinical trials.gov NCT03291951) are testing the effectiveness of resistance training to increase muscularity and thereby decrease dose-limiting toxicity and increase chemotherapy completion rates among colon cancer patients.

Breast cancer

Breast cancer is the most common cancer among women both in the UK[14] and the USA[15]. Obesity is a well-established risk factor for breast cancer incidence and survival, but as described previously, although studies have clearly shown worse mortality with obesity, the association between breast cancer survival and overweight (BMI 25–30) has been less consistent, with some studies showing no adverse effect[33–35]. BMI only incompletely captures the more relevant physiologic measures of skeletal muscle and adipose tissue.

Association with cancer recurrence and survival

We conducted the largest study of the association of measures of body composition with breast cancer survival in the non-metastatic setting published to date. The study population included 3283 breast cancer survivors diagnosed with stage II–III breast cancer from 2000 to 2012. Even in this non-metastatic community-based population, 34 % of subjects were sarcopenic (defined as skeletal muscle index (SMI) <40 cm^2/m^2). Patients with sarcopenia showed higher overall mortality (HR = 1·46; 95 % CI 1·23, 1·74), compared with those without. In addition, patients in the highest tertile of total adipose tissue also showed higher overall mortality (HR = 1·35; 95 % CI 1·08, 1·69), compared with those in the lowest tertile. The highest mortality was seen in the sarcopenic obese, those with both sarcopenia and high total adipose tissue (HR = 2·08; 95 % CI 1·44, 3·01). BMI alone had a much weaker association with mortality and incorrectly classified some women at risk for adverse outcomes due to body composition[36]. Three other studies also evaluated the associations between body composition and survival among non-metastatic breast cancer patients. Before our study, the previous largest study to date included 471 non-metastatic breast cancer patients (stage I–IIIA) and showed similar results with worse overall survival with sarcopenia measured by dual-energy X-ray absorptiometry (HR = 2·86; 95 % CI 1·67, 4·89). However, all muscle measurements were taken after chemotherapy treatment[37]. Del Fabbro *et al.* analysed data from 129 non-metastatic breast cancer patients treated with neoadjuvant chemotherapy at MD Anderson Cancer Centre, Texas, USA[38]. Sarcopenia was defined as SMI ≤38·5 cm^2/m^2 measured by CT. There was a trend towards an association between sarcopenia and the chance of pathologic complete response (OR = 4·97; 95 % CI 0·99, 16·87) in the overall population. When limited to patients with a normal BMI (defined as <25 kg/m^2), the odds for a response were higher among those with sarcopenia (OR = 6·86; 95 % CI 1·30, 36·04). Although sarcopenia was not associated with overall survival time, patients with sarcopenic obesity had shorter progression-free survival time[38]. The smallest study (*n* 119) found similar results with sarcopenia (defined as SMI <41 cm^2/m^2 measured on CT) significantly associated with worse disease-free ($P = 0·02$) and overall ($P = 0·05$) survival, whereas there was no significant association between BMI and survival[39].

Association with chemotherapy toxicity

Several studies have examined the associations between chemotherapy toxicity and body composition in early-stage breast cancer. In the largest study published to date, low SMI measured by CT was associated with a higher risk of any grade 3/4 toxicity ($P = 0·0002$) among 151 non-metastatic breast cancer patients receiving anthracycline and taxane-based chemotherapy. In addition, low skeletal muscle gauge (skeletal muscle index multiple by skeletal muscle radiodensity) was

https://doi.org/10.1017/S0029665118000423 Published online by Cambridge University Press

associated with a higher risk of grade 3/4 haematologic toxicity (relative risk = 2·12; 95 % CI 1·11, 4·04), grade 3/4 gastrointestinal toxicity (relative risk = 6·49; 95 % CI 1·42, 29·63) and hospitalisation (relative risk = 1·91; 95 % CI 1·00, 3·66), even after adjusting for age and body surface area[40]. Among eighty-four Asian breast cancer patients with non-metastatic breast cancer, higher levels of visceral fat was associated with a higher risk of grade 4 leucopenia ($P = 0·014$), whereas lower SMI was associated with a trend towards a higher rate of grade 3/4 leucopenia and neutropenia ($P = 0·051$)[41]. A smaller earlier study of twenty-four stage II–III breast cancer patients treated with epirubicin-based chemotherapy found that lower lean body mass was associated with higher risks of toxicity with differences in pharmacokinetics[42]. In combination, these studies suggest that measures of body composition are better predictors of chemotherapy-related toxicity than the widely used body surface area. However, none of these studies have looked at the efficacy of chemotherapy dosing based upon body composition parameters.

Intervention studies on body composition among breast cancer patients

In addition to being an important prognostic factor, body composition is also a potentially modifiable risk factor. Several trials have successfully demonstrated this approach in non-metastatic breast cancer patients. The largest study was a multicentre randomised trial of 200 subjects who were randomised to usual care (*n* 60), aerobic exercise training (*n* 64) or resistance exercise training (*n* 66) for the duration of adjuvant chemotherapy. Resistance training was more likely to increase skeletal muscle index and reverse sarcopenia than either usual care or aerobic exercise. Improvement in sarcopenia was also associated with a clinically meaningful improvement in quality of life and fatigue[43]. Another randomised trial compared a combined aerobic and resistance exercise programme *v.* usual care among 121 breast cancer survivors taking aromatase inhibitors and reported significant increases in lean body mass and decreases in body fat over 12 months[44]. Finally, in an exploratory study, twenty subjects were randomised to either a 16-week aerobic and resistance training programme *v.* delayed control. Exercise participants experienced significant improvements in lean body mass, percent body fat and fat mass. Inflammatory biomarkers and adipose tissue were examined at baseline and at end of intervention and also showed significant improvement in markers of inflammation with exercise[45].

Conclusions

Even among non-metastatic cancer patients, sarcopenia is highly prevalent. With the wide use of CT scans in cancer staging and diagnosis and the availability of software to automate the process, assessments of body composition should be incorporated as part of routine clinical assessments for patients with early-stage breast cancer and colorectal cancer given the strong associations with chemotherapy toxicity and complications and most importantly both disease-free and overall survival. Further research should also focus on deriving clinical cut-points for sarcopenia that will help to shape clinical care. Body composition measures can be a stronger predictor of surgical complications than BMI or weight and should be considered as part of pre-operative risk management. Body composition is strongly associated with chemotherapy toxicity and studies should be done in the metastatic setting to look at the efficacy of dosing based upon lean body mass since the goal of chemotherapy in the metastatic setting is palliative and not curative. Body composition is a modifiable factor, as has been shown in multiple randomised trials, and should be considered when designing both nutritional and physical activity interventions for cancer survivors.

Financial Support

Research funding was provided by the National Cancer Institute, Rockville, MD, USA (grant number 5R01CA184953-02).

Conflicts of Interest

None.

Authorship

Dr Elizabeth Cespedes Feliciano and Dr Wendy Y. Chen were joint authors on this manuscript and involved in all aspects of drafting, writing, and reviewing the final manuscript.

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Proceedings of the Nutrition Society

https://doi.org/10.1017/S0029665118000423 Published online by Cambridge University Press