

Prevalence of Sarcopenia in Cancer Patients: Review and Future Directions

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Abstract

Background: Sarcopenia, or skeletal muscle loss, is a common problem in post-treatment cancer patients and can negatively affect physical function and quality of life (QOL). This condition has recently received special attention in the cancer literature because it is associated with reduced physical activity and increased mortality in patients with cancer. The aim of this brief review was to evaluate the prevalence of sarcopenia in cancer patients.

Methods: A comprehensive literature search was conducted to examine the prevalence of sarcopenia in cancer patients. PubMed was searched for articles published from January 1950 to March 30, 2014, using the keywords 'sarcopenia or sarcopenic' AND 'cancer or malignancy or neoplastic'. For evaluating effectively the prevalence of sarcopenia, the search was limited to studies with a cross-sectional or longitudinal design.

Results: A total of 28 articles met the established criteria. These previous studies showed the prevalence of sarcopenia differed widely between different cancer diagnoses, ranging from 14%-78.7% based on the cancer diagnosis. Cancer patients with sarcopenia were found to have lower QOL, worsened fatigue, decreased physical function, and longer hospital stay relative to cancer patients without this condition.

Conclusion: Sarcopenia cancer patients may need physical exercise for improved physical function and QOL. Currently, few studies have been conducted on sarcopenia in cancer patients, and more studies are needed for investigating the prevalence of sarcopenia in these patients.

Keywords: Sarcopenia; Cancer; Cachexia; Prevalence; Physical exercise

Introduction

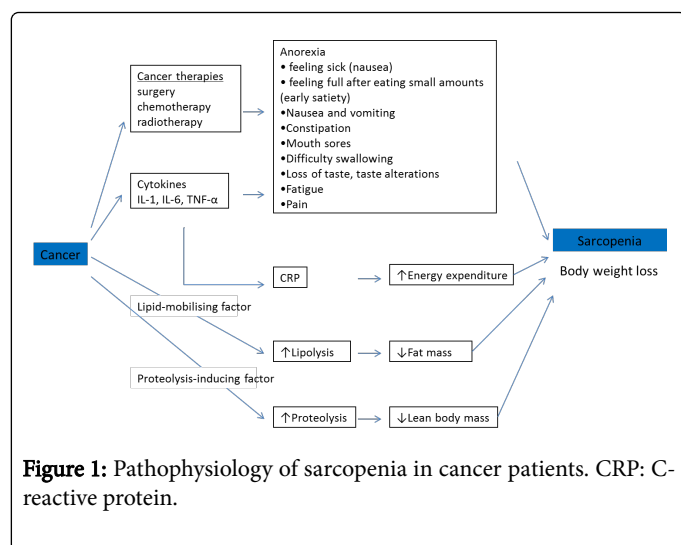
A majority of patients with advanced cancer often experience involuntary loss of weight [1], and a main cause of this condition is cancer cachexia. As a complex metabolic disorder, cancer cachexia is characterised by involuntary weight loss resulting from the depletion of skeletal muscle and adipose tissue, anorexia, fatigue, anaemia, and impairments in immune and endocrine functioning [2,3]. Further, since cancer cachexia is often accompanied by anorexia, it can lead to decreased physical function and psychological distress [4]. Up to 80% of people with cancer experience involuntary weight loss and loss of appetite [5], and these symptoms of cancer cachexia syndrome have been found to be associated with poor quality of life and morbidity [6,7]. However, although cachexia has been long recognised as an adverse effect of cancer [8], weight loss in patients with cancer is rarely recognised and assessed among hospital staff [9,10]. Moreover, patients with severe muscle wasting, on-going catabolism, low performance status, or metastatic disease refractory to therapy are presently unlikely to experience clinically important benefits from multimodal treatments intended to result in the gain of lean tissue mass and function [11]. Thus, cachexia represents an important unmet need. However, the collection of signs and symptoms of cachexia syndrome made the condition difficult to define, and thus far, cachexia syndrome is proving to be extremely challenging to treat effectively [12]. Because of the prevalence of cachexia among patients with advanced cancer,

researchers and clinicians have focused effort on evaluating and categorising cancer patients to allow early identification of those with a particularly high risk of developing this condition to enable more timely and proactive treatments [13]. Based on recent studies highlighting the role of muscle loss in cachectic cancer patients, the present international consensus includes skeletal muscle loss (also called sarcopenia) in the definition of cancer cachexia, irrespective of the loss of fat mass [14]. Cachexia is defined as a weight loss of >5% in individuals without previous muscle depletion or a weight loss of >2% in those having already shown depletion according to a current body mass index of <20 kg/m² or a loss of skeletal muscle mass [2]. Thus, sarcopenia must be considered as a key diagnostic criterion of cancer cachexia. The term sarcopenia is derived from the Greek meaning 'poverty of flesh' and is characterised by the progressive loss of skeletal muscle mass, muscle strength, and physical performance [15]. The predictive value of sarcopenia for health outcomes is related to the metabolic and functional relationship between muscle mass and physical strength, mobility, and vitality [16-18]. In particular, sarcopenia is associated with an increased risk for age-related decline in muscular strength and physical activity [19,20]. It was originally described in the elderly non-cancer population, and is often now defined as a geriatric syndrome associated with functional impairment, increased risk of falls, fractures, and reduced survival [16,21,22]. Recently, sarcopenia has received special attention in the cancer literature because it is associated with reduced physical activity and increased mortality in patients with cancer [23-25]. This review will (1) address the question of why cancer patients develop sarcopenia, (2) describe the modalities used for the assessment of lean body mass

(sarcopenia), (3) evaluate the prevalence rate of sarcopenia in cancer patients, and (4) discuss the need for physical exercise in sarcopenia patients and future directions.

Why do cancer patients develop sarcopenia?

Weight loss is frequent among cancer patients, especially in advanced disease, and is a feature of cancer cachexia (Figure 1) [2,14,26]. Weight loss is understood to be driven to varying degrees by low food intake (anorexia), which in turn may be the result of a wide variety of symptoms directly limiting oral intake (e.g. nausea, vomiting, mouth sores, loss of taste) or indirectly limiting it (e.g. pain, fatigue). Various metabolic and endocrine changes and activation of catabolic pathways account for some of the weight loss, which is typically greater than would be expected for the prevailing level of intake [27]. In some cancer patients, the elevation of cytokine levels (e.g. tumour necrosis factor- α , interleukin-1, interleukin-6) results in high C-reactive protein levels and thus increased energy expenditure, which can result in body weight loss [28]. Meanwhile, cancer patients also show increased lipolysis and proteolysis, which can lead to decreased lean body mass and fat mass, respectively [29]. Consequently, this increased proteolysis can result in or contribute to sarcopenia in many cancer patients. Recognition of these various problems by the physician and medical staff is important for dealing with cancer patients.



Assessment of lean body mass (sarcopenia)

In general, muscle mass or lean body mass is evaluated in cancer patients using 2 imaging techniques: mass-computed tomography (CT) and dual energy X-ray absorptiometry (DXA). CT is considered to be a very precise imaging approach that can separate fat from other soft tissues of the body, and thus CT methods are considered to be the gold standard for estimating muscle mass in cancer research. Meanwhile, DXA is an attractive and preferred alternative method for distinguishing fat, bone mineral, and lean tissues in both research and clinical settings because the patient is exposed to minimal radiation during the whole-body scan. However, bioimpedance analysis (BIA) estimates are often used to evaluate the volume of fat and lean body mass in elderly people [30,31]. Under standard conditions, BIA results have been found to correlate well with magnetic resonance imaging (MRI) predictions [32]. Further, prediction equations have been

validated for adults from various ethnicities [32]. However, in cancer research, CT assessments are typically performed for assessing sarcopenia and are preferred to BIA assessments. A general description of the basic CT, DXA, and BIA protocols and/or calculations for derived indices is provided below.

CT

CT has been shown to be accurate for the measurement of human body composition [33]. The regional muscle tissue is measured from electronically stored images, and the CT image analysis is typically performed as described previously [34]. In general, the third lumbar vertebra (L3) is chosen as a standard landmark [35], and 2 consecutive slices are assessed to measure the cross-sectional area of the muscle and adipose tissue [25,34]. The muscles at the L3 level comprise the psoas, erector spinae, quadratus lumborum, external and internal obliques, and rectus abdominis. Specific software is used to analyse the CT images (Slice-O-Matic V4.3 software; Tomovision, Montreal, Canada), and the skeletal muscle is identified and quantified by Hounsfield unit thresholds of -29 to $+150$ [33]. Cross-sectional areas (cm^2) of the sum of all of these muscles are computed, and the mean value for 2 consecutive images is calculated for each patient. The total lumbar skeletal muscle cross-sectional area (cm^2) and total lumbar adipose tissue area (cm^2) are linearly related to the whole-body muscle and adipose tissue mass [34,36]. These values are normalised for stature as is conventional for BMI and body composition components [25,34] and expressed in units of cm^2/m^2 . Sarcopenia is defined as a cut-off point of $\leq 38.5 \text{ cm}^2/\text{m}^2$ in women and $\leq 52.4 \text{ cm}^2/\text{m}^2$ in men for the lumbar skeletal muscle index [25].

DXA

DXA was recently validated as a precise method for the clinical assessment of sarcopenia in cancer patients [37]. An appendicular lean mass index is calculated by dividing the appendicular lean mass (kilogram) by the height (meter) squared [16]. Sarcopenia is defined as 2 standard deviations below the mean appendicular lean mass index value of young healthy females ($<4.45 \text{ kg}/\text{m}^2$) and young healthy males ($<7.26 \text{ kg}/\text{m}^2$) [15,16].

BIA

The BIA system was designed to collect multiple sets of whole-body and segmental impedance measurements without requiring conventional gel electrodes. The BIA device provides measurements of impedance ($\pm 1 \Omega$) and estimates of fat mass ($\pm 0.1 \text{ kg}$) and lean body mass ($\pm 0.1 \text{ kg}$). The measurements are carried out at a frequency of 50 kHz with 0.5 mA. Skeletal muscle mass is calculated using the following BIA equation [32]: Skeletal muscle (SM) (kg) = $[0.401 \times (\text{height}^2/\text{resistance}) + (3.825 \times \text{gender}) - (0.071 \times \text{age}) + 5.102]$, where height is in cm; resistance is in ohms; the gender values for men and women were taken as 1 and 0, respectively; and age is in years. The absolute SM is converted to an SM index (SMI) by dividing the value by the height in meters squared (kilograms/meter squared). Sarcopenia is defined using the cut-offs for men and women ($<8.87 \text{ kg}$ and $<6.42 \text{ kg}$ skeletal muscle mass/ m^2 , respectively) as determined by Chien et al. [31].

Prevalence of Sarcopenia among Cancer Patients

Literature search

Data source: PubMed was searched for articles published from January 1950 to March 30, 2014, using the keywords 'sarcopenia or sarcopenic' AND 'cancer or malignancy or neoplastic'. The limitations 'human' and 'middle-aged and aged (>45 y)' were applied to the search parameters, and 'child or children' were used to exclude articles.

Study selection: To evaluate effectively the prevalence of sarcopenia, we limited this search to studies with a cross-sectional or longitudinal design. Acceptable methods of body composition assessment included CT scan, DXA, and BIA.

The prevalence rate of sarcopenia in cancer patients

A total of 28 articles met all the established criteria (Table 1). Since 2009, 28 studies have reported the occurrence of sarcopenia in various cancer patients, including those with breast, pancreatic, oesophagogastric, lung, hepatocellular, biliary tract, colorectal, renal cell, haematological, and mixed cancers. The number of patients in these studies ranged widely from 28-599, and an approximate age range of 50-66 years was observed in many studies. For the assessment of sarcopenia, 24, 3, and 1 study used CT, DXA, and BIA analysis, respectively. The prevalence of sarcopenia in cancer patients ranged from 14%-78.7% and differed between patients according to cancer type. Many of the cancer patients had sarcopenia. For breast cancer patients, these previous studies reported a prevalence of 14%-25.5% [24,37-39]. Similarly, a prevalence of 55.9% and 63% was reported for pancreatic cancer patients [40,41]. Meanwhile, sarcopenia occurred at a prevalence of 26% and 57.4% for pre-chemotherapy oesophagogastric cancer and 43% and 78.7% for post-chemotherapy oesophagogastric cancer, respectively [42,43]. In addition, the prevalence was 46.8% for non-small cell lung cancer [44], 27.5% and 30% for hepatocellular carcinoma [45,46], 40% for cirrhosis [47], 16%-

67.5% for liver tumours post-liver resection [48-51], 35.7% for biliary tract cancer [52], 38.9% for colorectal cancer [53], 52.5% and 54.5% for renal cell cancer [35,54,55], 38.5% for bladder cancer after radical cystectomy [56], 50.6% for haematological cancer [57], and 35.7%-51% for mixed cancer [23,58-60]. As indicated by these previous findings, the prevalence of sarcopenia differed according to the cancer diagnosis. In particular, the prevalence of sarcopenia was higher in patients with pancreatic cancer and oesophagogastric cancer [40-43], but tended to be lower in patients with breast cancer [24,37-39]. As such, sarcopenia might develop more frequently in patients with gastrointestinal cancer. To date, no study has reported the prevalence of sarcopenia according to the stage of cancer. Moreover, of the many studies examined in the present article, few reported the cancer stage of the patients. Hence, the relation between the prevalence of sarcopenia and cancer stage could not be evaluated in the present article. One report showed that male cancer patients are more susceptible to sarcopenia than female [57]; however, other reports do not show the prevalence of sarcopenia differ to gender. In cancer patients, whether sarcopenia in cancer patients could not be confirmed in the present article. Although sarcopenia is generally related to age, no study has shown an association between the prevalence of sarcopenia and age in cancer patients. Elderly cancer patients might be more likely to develop sarcopenia, but the findings from the various reports were insufficient to derive conclusions with respect to this potential association. Prado et al. [24] have discussed chemotherapy toxicity-induced sarcopenia in breast cancer patients, while Awad et al. [42] and Connie Yip et al. [43] found that the prevalence of sarcopenia was increased for post-chemotherapy patients as compared to pre-chemotherapy patients. Correspondingly, many studies have shown that chemotherapy is associated with sarcopenia [38,40,45,55]. On the other hand, 2 studies showed that chemotherapy had no influence on the prevalence of sarcopenia in cancer patients [23,41]. Although no firm conclusions can be made on the basis of the present reports, the prevalence of sarcopenia tends to be higher in post-chemotherapy patients as compared to pre-chemotherapy patients.

Article (year of publication)	Patients N (M/F)	Age (years; mean or median)	Tumor, Stage	Method of measurement	Prevalence of sarcopenia	
					N	%
Prado et al. [24]	55 (0/55)	55, mean	Breast cancer, Stage NR	CT of L3	14	25.5%
Villaseñor et al. [37]	471 (0/471)	NR	Breast cancer, Stage I-III	DXA whole-body	75	16%
Del Fabbro et al. [38]	129 (0/129)	NR	Breast cancer, Stage I-III	CT of L3	18	14%
George et al. [39]	599 (0/599)	57.5, mean	Breast cancer, Stage 0-III	DXA whole-body	84	14%
Dalal et al. [40]	41 (18/23)	59, mean	Pancreatic cancer, Stage NR	CT of L3	26	63%
Tan et al. [41]	111 (52/59)	64, mean	Pancreatic cancer, Stage II-IV	CT of L3	62	55.9%
Awad et al. [42]	47 (34/13)	NR	Oesophagogastric cancer, Stage 0-III	CT of L3	27, pre-chemotherapy	57.4%
					37, post-chemotherapy	78.7%

Yip et al. [43]	35 (30/5)	63, mean	Oesophagogastric cancer, Stage 0-III	CT of L3	9, pre-chemotherapy	26%
					15, post-chemotherapy	43%
Baracos et al. [44]	441 (229/212)	66, mean	Non-small cell lung cancer, Stage III-IV	CT of L3	206	46.8%
Mir et al. [45]	40 (30/10)	62.5, median	Hepatocellular carcinoma, Stage NR	CT of L3	11	27.5%
Meza-Junco et al. [46]	116 (98/18)	58, mean	Hepatocellular carcinoma, Stage I-IV	CT of L3	35	30%
Montano-Loza et al. [47]	112 (78/34)	54, mean	Cirrhosis, Stage NR	CT of L3	45	40%
Harimoto et al. [48]	186 (145/41)	66, mean	Post-hepatectomy for hepatocellular carcinoma, Stage I-IV	CT of L3	75	40.3%
Dello et al. [49]	40 (24/16)	62, median	Post-liver resection for liver tumours, Stage NR	CT of L3	27	67.5%
van Vledder et al. [50]	196 (120/76)	64.5, median	Post-liver resection for colorectal liver metastases, Stage II-III	CT of L3	38	19.4%
Peng et al. [51]	259 (155/104)	58, mean	Post-liver resection for colorectal liver metastasis, Stage NR	CT of L3	41	16%
Mir et al. [52]	28 (19/9)	63, median	Biliary tract cancer, Stage NR	CT of L3	10	35.7%
Lieffers et al. [53]	234 (135/99)	63, mean	Colorectal cancer resection, Stage II-IV	CT of L3	91	38.9%
Huillard et al. [54]	61 (38/23)	60, median	Renal cell cancer, Stage NR	CT of L3	32	52.5%
Antoun et al. [55]	80 (NR/NR)	60, mean	renal cell carcinoma, Stage NR	CT of L3	42	52.5%
Antoun et al. [35]	55 (37/18)	59, mean	renal cell carcinoma, Stage NR	CT of L3	30	54.5%
Smith et al. [56]	200 (141/59)	66, median	Radical cystectomy for bladder cancer, Stage 0-III	CT of L3	77	38.5%
Morishita et al. [57]	164 (100/64)	50, median	Haematology cancer, Stage NR	BIA	83	50.6%
Veasey-Rodrigues et al. [58]	16 (11/5)	60, median	Mixed cancer including endometrial, ovarian, cervical, non-small cell lung, colorectal, melanoma, anus, Stage NR	CT of L3	7	44%
Parsons et al. [59]	104 (65/39)	NR	Mixed cancer including gastrointestinal, head/neck, and other, Stage NR	CT of L3	53	51%
Prado et al. [23]	28 (19/9)	65, mean	Mixed cancer including advanced non-small cell lung cancer (Stages IIIB or IV) and colorectal cancer (Stage IV)	DXA whole-body	10	35.7%

Parsons et al. [60]	48 (19/29)	56, mean	Mixed cancer including colorectal, melanoma, ovarian, breast, cholangiocarcinoma, and other, Stage NR	CT of L3	20	42%
DXA: Dual-energy X-ray Sbsorptiometry; CT: Computed Tomography; L3: Third Lumbar Vertebrae; BIA: Bioimpedance Analysis; NR: Not Recorded.						

Table 1: Prevalence of sarcopenia among cancer patients.

Physical condition and outcomes of cancer patients with sarcopenia

Survival rate: Some studies reported the survival rate was significantly worsened in cancer patients with sarcopenia as compared to that in cancer patients without this condition [46-48,50,52,59,61]. Furthermore, sarcopenic cancer patients with obesity had a decreased survival rate relative to those without sarcopenia [25,40,41]. In contrast, some reports found that sarcopenia was not associated with survival in cancer patients [43,45,51,56,60]. Although the influence of sarcopenia on the survival rate in cancer patients remains to be resolved, a sufficient number of studies suggest that sarcopenia might adversely affect survival in this group of patients.

Quality of life: Thoresen et al. [62] showed that in advanced colorectal carcinoma, patients with sarcopenia have substantial financial difficulties compared to those without sarcopenia. Further, other reports have shown that cancer patients with sarcopenia have significantly lower scores for physical functioning, bodily pain, and vitality in health-related QOL than those without sarcopenia [57]. Although few reports have observed the presence of these relationships, sarcopenic cancer patients might tend to have worsened QOL compared to those without sarcopenia.

Fatigue: One study reported that cancer patients with sarcopenia had significantly increased fatigue compared to those without sarcopenia [57], while other studies have not observed this association. Hence, at present, it is not possible to make conclusions about the relationships between sarcopenia and fatigue in this group of patients.

Physical function: The average handgrip strength was greater in cancer patients without sarcopenia than in those with this condition. However, no differences were observed in the 2-minute or 6-minute walk tests between the 2 groups [23,57]. Because sarcopenic cancer patients have muscle weakness, these patients might tend to have decreased muscle strength as compared to cancer patients without sarcopenia. However, this muscle weakness might not be related to exercise capacity.

Rehabilitation care and length of stay: For colorectal cancer patients, sarcopenia was significantly associated with inpatient rehabilitation care and consequently a longer length of stay [53]. Sarcopenic patients who underwent liver resection for colorectal liver metastasis were more likely to have a longer overall hospital stay compared to non-sarcopenic patients [51]. Lieffers et al. [53] found that sarcopenic cancer patients more commonly received rehabilitation. The increased muscle weakness in sarcopenic cancer patients might lead to lower functioning for activities of daily living, and thereby result in longer hospital stays and an increased need for rehabilitation as compared to those without sarcopenia.

Exercise for Sarcopenia in Elderly People: General Concept

Resistance exercise interventions are associated with significantly greater increases in lean body mass in aging adults compared to other exercise interventions [63], and is performed for sarcopenia in elderly people. Based on the results of the Cochrane review [64,65], patients who participated in progressive resistance exercise were likely to show meaningful strength gains, along with decreases in physical disability. Older adult patients are likely to benefit from supervised progressive resistance training, regardless of the setting or mode of training. Hence, progressive resistance training should be encouraged among healthy adults to minimise degenerative muscular function associated with aging [66]. Physical training when delivered as resistance training has the ability to elicit hypertrophy and increase muscle strength in very elderly muscles [67].

Exercise Recommendations for Cancer Patients with Sarcopenia

To date, no research has examined the effects of exercise on sarcopenia in cancer patients. In general, cancer patients perform resistance and aerobic exercises in the same capacity as elderly people [68-71]. The American College of Sports Medicine recently concluded that exercise is safe for cancer survivors, that all cancer survivors should avoid inactivity (i.e. exercise is recommended), and that exercise programs should be adapted for the individual survivor on the basis of health status, type of cancer treatment, targeted health outcomes, and disease trajectory [72]. In a systematic review, progressive resistance training was observed to have a positive effect on lean body mass and likely to be relevant for post-treatment cancer patients [73]. Similarly, a systematic review showed that physical exercise (aerobic, resistance, or a combination of both) had a positive effect on muscle mass and strength in cancer patients with different types and stages of cancer disease [74]. Meanwhile, a systematic literature review found that resistance and strength training programs for cancer survivors had marginal benefits with respect to quality of life [75] and fatigue [76] in cancer patients. Many articles have stated the importance of exercise in cancer patients, and more resistance and strength exercises might be needed for improving muscle function in sarcopenic cancer patients as compared to those without sarcopenia. The improvement of physical function in sarcopenic patients could lead to higher QOL and decreased fatigue.

Conclusions and Future Research

We reviewed the research on sarcopenia in relation to patients with different types of cancer and found that the reported prevalence differed between cancer types. However, few studies have yet been performed in this particular field, and more future studies are needed

for investigating the prevalence of sarcopenia in patients with cancer. Similarly, additional studies should be performed to investigate the role of progressive resistance training for sarcopenia in cancer patients and the influence of physical exercise on physical function, quality of life, and fatigue in these patients. We recommend exercise for cancer patients with sarcopenia and informing them that exercise does not aggravate the cancer. Cancer patients with sarcopenia should be told that even low amounts of exercise are better than activity and that exercise can provide additional benefits.

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