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Published in:
Current Opinion in Clinical Nutrition and Metabolic Care

DOI:
10.1097/MCO.0000000000000648

Published: 01/05/2020

Document Version:
Peer reviewed version

Licence:
Other

Current Opinion in Clinical Nutrition and Metabolism

Word count : 2523

Title of Review Article:

Fish Oil Supplementation and Maintaining Muscle Mass in Chronic Disease: State of the Evidence

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Abstract (196 words)

Purpose of Review*:* Providing EPA and DHA, in the form of fish oils, to benefit muscle is an emerging area of interest. The aim of this work was to evaluate the current literature that has assessed muscle mass as an outcome during a fish oil intervention in any chronic disease.

Recent Findings: The vast majority of studies published in the last 3 years (12 out of 15) have been conducted in the oncological setting, in patients undergoing treatment for cancers of the gastrointestinal tract, breast, head and neck, lung, cervix and hematological cancers. Three studies were conducted in patients with COPD. Fish oil was provided as part of a nutrient mixtures in 12 studies and as capsules in 3 studies.

Summary: Overall the evidence for an effect of fish oil supplementation on muscle mass in cancer patients undergoing treatment and in COPD remains unequivocal and reveals nothing new in the area of fish oil supplementation in the cancer setting which continues to provide mixed evidence on the efficacy of fish oil on muscle mass and function. This review highlights challenges in comparing and interpreting current studies aimed at testing fish oil supplementation for muscle health.

Key Words:

Skeletal muscle, EPA, DHA, clinical trials

Abbreviations

RCT	Randomised Controlled Trial
PUFA	PolyUnsaturated Fatty Acids
ONS	Oral Nutritional Supplement
RA	Rheumatoid Arthritis
GI	Gastrointestinal
DXA	Dual x-ray Absorptiometry
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
COPD	Chronic Obstructive Pulmonary Disesase
BIA	Bio-Impedance Analysis

Introduction

Chronic disease generally occurs in older individuals and exacerbates the normal physiology of aging which includes muscle loss. Chronic disease is generally associated with some degree of inflammation and altered hormone regulation impacting muscle health (1). Low muscle mass is a feature common to many chronic diseases, and often exists even at the time of diagnosis, with additional losses anticipated during the trajectory of chronic disease evoked by the disease process itself or the medications prescribed for managing the condition (2, 3). Sedentary lifestyles and poor diets may also contribute to the development of chronic disease and have a negative impact on muscle health.

Sarcopenia, or muscle mass below a specific threshold that is associated with disability, has received attention in recent years due to its association with poor outcomes in nearly all chronic diseases in which it has been evaluated. A more recent poor prognostic factor of low muscle attenuation (low muscle radiodensity) has been revealed by the opportunistic application of CT imaging and is associated with aberrant fat infiltration into muscle (4, 5). There have been several recent reviews on the association of body composition features with poor outcomes in aging (6), cancer (3), and chronic liver disease (7, 8). However, less is known about how to potentially modify these poor prognostic features with nutritional interventions.

Dietary n-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), have well described immune-modulating effects, and have been studied with respect to modification of the burden of chronic disease. EPA and DHA are nutrients found in fatty fish and their oils, and can be encapsulated or provided as a component of oral nutritional supplements. This review evaluates recent evidence (published in the past three years) to determine whether provision of EPA and DHA, in the form of fish oil, is associated with improved muscle mass and/or function in chronic diseases.

Rationale for Study of EPA and DHA in Muscle Health

A handful of elegant studies have yielded positive results with respect to an attenuation of aging associated muscle loss when EPA and DHA are provided to older individuals. During healthy aging, n-3 PUFA supplementation improves muscle protein synthesis, strength and function as well as muscle mass (9, 10) in the absence of changes in inflammation. Pathways that have been explored include insulin stimulated pathways and mitochondrial function, both of which are enhanced in older humans supplemented with n-3 PUFA (11, 12). In conditions of insulin resistance, also common to many chronic diseases, n-3 PUFA improve insulin sensitivity even in the absence of gains in muscle mass (12-14). Nearly two decades of research in the cancer setting has additionally provided mixed evidence on the benefit of providing fish oil for maintenance of muscle mass (15, 16).

Status of n-3 fatty acids and Low muscle mass are generally independently evaluated in chronic diseases

Poor status of n-3 PUFA has been reported in many chronic diseases where low mass muscle mass has been reported separately including Rheumatoid Arthritis (RA) (17), Chronic Obstructive Pulmonary Disease (COPD) (18-20), liver disease (Non Alcoholic Fatty Liver Disease and cirrhosis) (21, 22); cancer (23-25); diabetes (17, 26, 27), Chronic Kidney Disease (28), Heart Disease (29) and Alzheimer's disease (30-32). The two features of poor n-3 PUFA status and low muscle mass may be related events rather than isolated events (23). Studies that have evaluated nutritional interventions with fish oils typically evaluate disease markers, and/or inflammation. These outcomes are rarely evaluated in tandem with body composition. Further, to our knowledge, no study has directly investigated mechanisms of action of EPA and DHA to evaluate a change in muscle protein synthesis and protein breakdown in a chronic disease condition.

Update on n-3 PUFA interventions in Chronic Disease where Muscle is Assessed as an outcome

A broad search of the literature over the past three years revealed 15 studies that have applied an n-3 PUFA intervention and measured muscle or lean body mass as an outcome. Twelve of these studies were conducted in the oncology setting; the additional three studies were conducted in COPD. Therefore, a major gap in the literature are studies that assess muscle mass during an n-3 PUFA intervention in other chronic diseases associated with muscle loss, such as RA and liver disease.

Cancer

The majority of people diagnosed with cancer experience muscle loss during their disease trajectory. The importance of maintaining muscle mass in the oncology setting is well established (33, 34). Loss of muscle is accelerated in cancer due to tumor metabolism, delivery of toxic drugs and limited food intake. N-3 PUFA supplementation studies in patients undergoing active treatment published since the early 2000s documented benefits on tumor response, prevention of toxicities, inflammation and maintenance of muscle mass (15, 35, 36). Studies published in the past three years were conducted in patients gastrointestinal (4 studies), head and neck (3 studies), breast cancer (2 studies), lung (1 study), cervical (1 study) and hematological cancer (1 study; Table 1).

<u>Gastrointestinal Cancers</u>

Four studies were conducted in patients with gastrointestinal cancer, including gastric, pancreatic and colorectal cancer, undergoing neoadjuvant chemotherapy or surgery. Sample sizes ranged from 20-34 per group. None of the studies evaluated outcome measures separately for men and women. The age of the participants varied from 30 y to 90 y to include a broad range of expected

muscle mass. All nutritional interventions for GI cancers used mixtures containing EPA and DHA, with three studies applying an ONS, and one study using capsules to provide fish oil alone or in combination with vitamin D. Two of three studies using an ONS provided additional calories and protein compared to the "control" intervention (37-39), one study (40) matched the control group with an equivalent amount of calories and protein. Compliance to the supplement was either not reported or reported to be a challenge impeding interpretation of the results. Results were varied with no effect, weight gain and increase in muscle mass being reported following the intervention. In the single study that used capsules containing vitamin D and fish oil, four groups were evaluated: 1) placebo, 2) fish oil, 3) vitamin D and 4) fish oil plus vitamin D. For each group, placebo capsules were provided. This study reported an increase in fat free mass in the fish oil groups (with and without vitamin D) (41).

Head and Neck Cancer

All of the studies conducted in the head and neck population used a nutrient mixture in the form of ONS. Two of the studies were comparable with respect to the supplement provided as well as duration of the intervention (42, 43). Neither of these studies showed an effect of supplementation on any of the assessed parameters. The third study provided ONS containing EPA and DHA during 6 weeks of treatment (44). Using a similar dose as other studies (2 g EPA/d), this group showed a stabilization of body weight and lean body mass, whereas the control group lost both weight and lean body mass. The intervention group also experienced an improvement in fatigue and measures of inflammation. Results of these studies are reported as a change over time in the intervention group rather than between groups as intended. Poor compliance to ONS is expected in this group experiencing a high symptom burden, although this was not assessed in the studies reviewed.

Breast Cancer

Two randomised controlled trials (RCTs) evaluated EPA and DHA in breast cancer patients; one during a chemotherapy regimen (45) and one in treatment naive patients awaiting surgery (46), therefore the intervention duration was different between the studies. Both studies provided EPA and DHA in the form of capsules. No changes in fat free mass neither during the intervention nor between the groups was observed (45, 46).

Other cancers

The other cancer categories included malnourished cervical cancer patients (47), weight losing NSCLC patients (48), and patients with mixed types of hematological malignancies (49). In cervical cancer patients, no absolute difference between intervention groups was reported for lean body mass (47). Laviano et al. reported no difference in lean body mass between a group of NSCLC patients receiving a nutrient mixture containing EPA and DHA compared to a placebo. Chagas et al. reported greater mid arm muscle

circumference in hematological cancer patients prescribed fish oil capsules during 9 weeks of treatment. Reporting results as a function of compliance resulted in small sample sizes in each subgroup.

Chronic Obstructive Pulmonary Disease (COPD)

Three studies in the past 3 years evaluated an n-3 PUFA supplementation in COPD patients, albeit having very different study designs (50-52). Calder et al. provided two containers of an ONS containing 1200 mg DHA and 800 mg EPA per day. Plasma n-3/n-6 ratios showed 79% of the intervention group achieved compliance. Improvements in symptoms (fatigue, dyspnea, walking distance) were observed, however, there were no changes in inflammation markers, activity scores, appetite or muscle mass after a 12 week intervention (50).

A second study in COPD patients in an open label study design provided a fish oil containing ONS during hospitalization for an acute phase of disease activity. On average, patients were hospitalized for one week and remained on the supplement until discharge. Longer hospital stay (receiving more supplements over time) was positively correlated with lean body mass (51).

A third study was conducted in COPD patients with low muscle mass who were undergoing rehabilitation on an outpatient basis. The nutritional intervention was comprised of a mixture of EPA and DHA, with leucine and vitamin D provided for 4 months concurrent with an intense exercise program. The control group received a placebo drink, therefore groups were not matched for calories or protein. Importantly, however, this study assessed the plasma levels of EPA and DHA at baseline and also compared these values to healthy controls. Both groups receiving n-3 PUFA experienced improved skeletal muscle mass, quadriceps muscle strength and cycle endurance time, inspiratory muscle strength only improved in the supplement group. Therefore there was an effect on function without a change in muscle mass (52).

Summary of Recent Literature

The studies applying fish oil interventions to evaluate effects on muscle health are currently almost exclusively been conducted in the oncology setting. Collectively, the literature over the past 3 years conducted in cancer and COPD does not strengthen the evidence base to support fish oil intervention to maintain muscle mass and there were no two studies that were similar in intervention, disease state, and outcomes. In general, studies suffer from limited, and often unjustified sample sizes where subgroup effects (such as age, sex or tumor site) are not able to be explored. A limitation in the ability to interpret studies also lies in the reporting of a change within the supplemented group over time, whereas in a RCT design, the difference between the two groups should be evaluated. Studies

reporting change over time in the intervention group when a difference between groups was not observed causes a bias to overestimate effects. Study design considerations for future studies are highlighted in Figure 1.

The prescribed dose of n-3 PUFA is generally reported, but not the actual dose taken. Only 4 out of 15 studies reported a biological measure of compliance. The prevailing literature suggests that an effective dose of fish oil is approximately 2 g per day (15, 16, 53-55), but whether that is total n-3, EPA and/or DHA remains to be determined. Dose justification is not referenced in the majority of reviewed studies and some used a lower dose (e.g. 1 g EPA per day). Poor compliance to fish oil containing supplements has been known for >15 years, therefore not having a measure of compliance is problematic. When there is no biological measure of compliance, one cannot relate the outcome measure to a specific amount of EPA or DHA achieved during the supplemental period. This information is required to enable an estimation of the required amount of EPA and DHA required to see a benefit should one exist. This remains a major gap in the area of nutritional supplementation studies. Importantly, EPA and DHA are dietary essential nutrients and patients with cancer (56) and COPD (52) have levels of EPA and DHA that are lower than comparable controls in the healthy population, which could be a result of the disease process, altered metabolism, poor diets, or a difference in essential fatty acid requirements. With the absence of plasma measures of n-3 fatty acids, it is challenging to know whether EPA and DHA are "supplemented" or restored nor do we know the level required to see a biological impact on the outcome of interest.

Studies showed no attention to or mention of age, sex or co-morbidities. Having specific diagnoses that affect muscle is often an exclusion criteria for entry into RCT that evaluate muscle mass. However, apart from diagnosed diseases per se, cancer patients are known to have one or more comorbidities at presentation (57). This contributes to poor muscle condition (58) in addition to the medications prescribed to manage those conditions. None of the studies evaluated men and women separately. It is known that there is considerable sexual dimorphism in muscle responses and responses to interventions (59-61). In order to better understand who is most likely to benefit from interventions, the analysis needs to account for this. Food intake and EPA and DHA intake from other sources is rarely assessed, even though the baseline diet is a key consideration in whether or not a person may respond to supplemental EPA and DHA. Further, adequate energy and muscle building nutrients are required to reach an anabolic response.

Perhaps even more important than muscle mass, is muscle function. Two studies that included an evaluation of muscle function showed a benefit. No study evaluated mechanisms although some associations of muscle mass with markers of inflammation in the blood were attempted recognizing inflammation to be driving muscle loss in chronic disease. The majority of studies applied bio-impedance analysis (BIA) to measure their primary outcome of muscle mass or lean body mass, however, BIA assesses fat free mass (including bone, organs and muscle) and not specifically skeletal muscle mass.

Conclusion

The set of literature published in the past 3 years does not strengthen the base of mixed evidence that has built over the past decades investigating muscle loss that occurs in chronic disease. The literature continues to provide mixed evidence on the efficacy of EPA and DHA for muscle mass and only reports on studies conducted in COPD and cancer. ESPEN guidelines for oncology patients recommend the use of fish oil supplements during cancer treatment and in patients expected to experience muscle loss however, this recommendation is based on weak evidence. The most recent systematic review effects of fish oils in the cancer setting concluded that provision of fish oils concurrent with chemotherapy is beneficial to body composition, an effect only seen in well-designed studies (15, 53). As has been previously reported, the safety and lack of harm from of n-3 PUFA supplementation was evident. However, to obtain more evidence base, RCTs in large, homogenous groups are needed. This can be achieved by forging collaborations between research groups and clinicians and to conduct multi-centre trials to enhance the evidence required to move from weak evidence regarding nutritional interventions in chronic diseases.

Key points

- Few studies outside of oncology have applied fish oil supplementation in tandem with measures of muscle mass
- Due to study design limitations, the evidence base on the benefit of fish oil on muscle mass is not enhanced by recently published research
- Clinical trials applying fish oil supplementation currently do not account for expected differences in age, sex, dietary intakes and co-morbidities as contributors to muscle mass
- Reporting on and measuring compliance remains an obstacle to building an evidence base in the area of fish oil supplementation in chronic disease

Figure Legends

FIGURE 1: A checklist of considerations for future studies designed to assess a nutritional intervention on muscle mass in chronic disease.

Acknowledgements

We would like to thank Dr. Liz Isenring and Dr. Lisa Martin for their critical review of the manuscript.

Financial Support

Faculty of Health Sciences and Medicine, University of Bond, Visiting Academic Award

Conflicts of Interest

The authors have no conflict of interests to declare.

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25 (Pratt et al, 2002)

**References of special interest:*
33 (Fearon et al, 2013), 58 (Xiao et al, 2018), 56 (Murphy et al, 2012)

References of outstanding interest:**
3 (Shachar et al, 2016), 5 (Bhullar et al, 2020), 15 (de van der Schueren et al, 2018)

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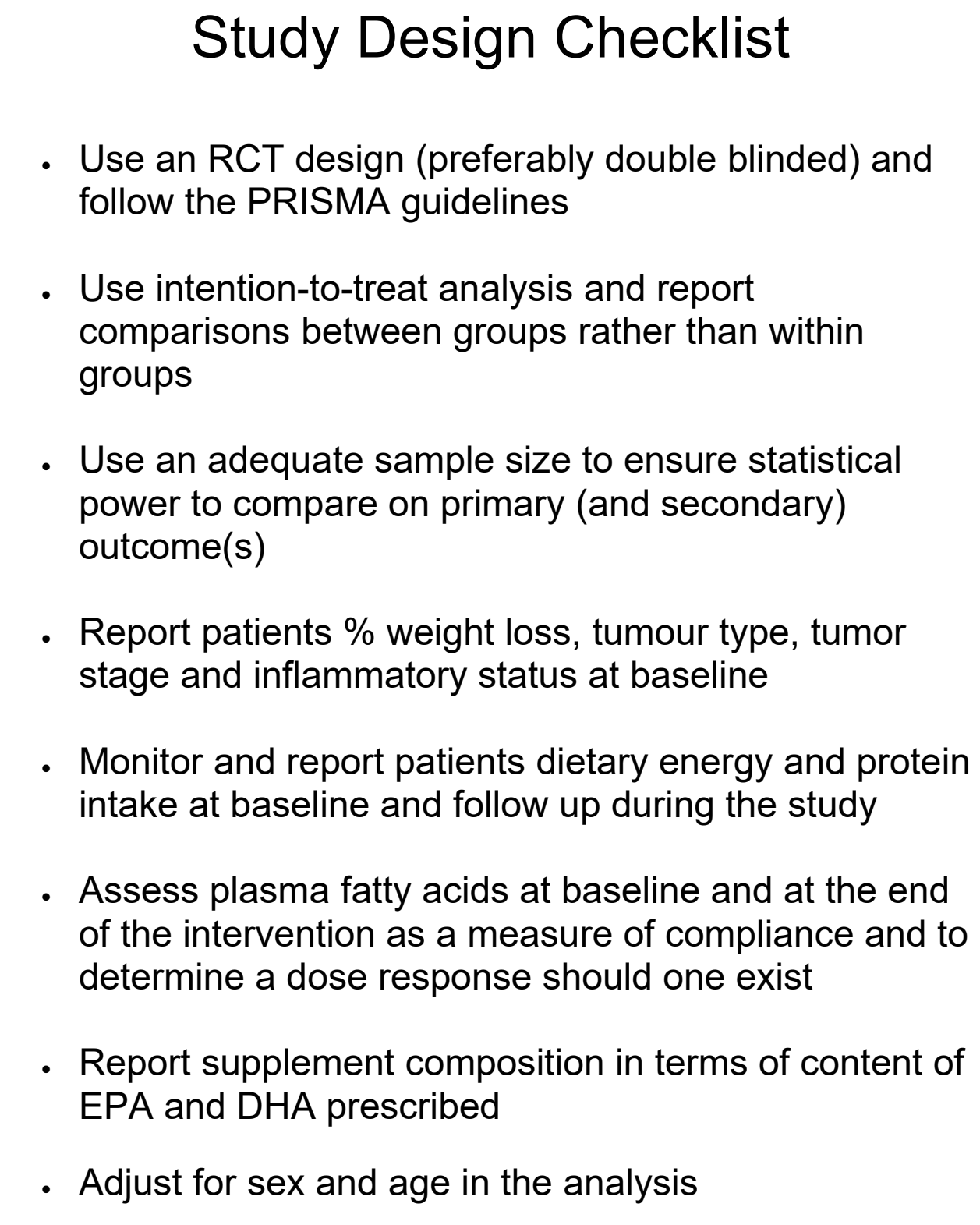
Figure 1. Study Design Checklist



Reference	Study design	Patient Population and Sample Size	Age[a] / Sex[b] Distribution	EPA/DHA (mg/d) Prescribed	Type	Control Group	Duration	Primary Outcome(s)
Gastrointestinal Cancers								
Feijo et al., 2019	RCT [open label]	Gastric cancer patients prior to surgery (n=66)	56% between 40-60y; 44% were >60y 44M:22F	EPA: 2200 DHA: 900	ONS	Standard ONS	30 days	Weight
Akita et al. ,2019	RCT	Pancreatic cancer, receiving neoadjuvant chemoradiation therapy containing gemcitabine. (n=62)	67.8 + 10.7y 11M:20F	EPA: 2200 DHA: 900	ONS	Regular Diet	5 weeks	Pre/post ratios of skeletal muscle mass and psoas muscle area
Aoyama et al., 2019 & Ida et al., 2017	RCT [multi-center open label phase III]	Gastric cancer (Roux en Y) surgery (n=60)	30-80 y 43M:17F	EPA : 2200 DHA: 900	ONS	Regular Diet	pre-operatively for 6 days plus 21 days post surgery after oral intake resumed	Lean body mass
Haidari et al., 2019	RCT	Colorectal cancer, n=80 (3 intervention groups with fish oil ± vitamin D and a control group; n=20/group)	56.7 ± 12.5 y 46M:35F	EPA: 1100 DHA: 500	Capsules	Placebo	2 Capsules/d for 8 weeks (with and without vitamin D) versus placebo	Inflammatory markers and nutritional status
Head and Neck Cancer								
Hanai et al., 2018	RCT	Weight losing head and neck cancer (n=27)	45-77 y 16M:11F	EPA : 2200 DHA: 900	ONS	Standard ONS	14 days prior to surgery and 14 days after	Nutritional status

Jantharapattana et al., 2018	RCT	Head and neck cancer undergoing curative surgery (n=65)	55.2 ± 13.5 y 60M:12F	EPA: 2200 DHA: 900	ONS	Standard ONS	7 days prior to surgery and 14 days post operatively	Weight
Solis-Martinez et al., 2018	RCT	Head and Neck cancer (n=64)	59 ± 14y 35M:29F	EPA: 2000 DHA: ?	ONS	Isocaloric Control	6 weeks	Body composition; inflammation
Breast Cancers								
De la Rosa et al., 2019	RCT	Breast Cancer Patients undergoing neoadjuvant therapy. (n=53)	28-72y Female	EPA: 1600 DHA: 800	Capsules	Placebo capsules	6 months	Body composition
Paixao et al., 2017	RCT	Treatment Naive Breast cancer patients (n=37)	40-60y Female	EPA: 940 DHA: 780	Capsules	Mineral oil capsules	30 days prior to surgery	Nutritional status
Other Cancers								
Aredes et al., 2019	RCT	Cervical cancer patients Treatment naive and those who had undergone curative treatment were included (n=40)	19-59 y Female	EPA: 2000 DHA: 500	Capsules	Placebo capsules		Skeletal muscle quantity and high-density skeletal muscle area
Laviano et al, 2019	RCT [Pilot]	Weight losing NSCLC patients undergoing first line chemotherapy (n=54)	64.4±7.7 y 38M: 17F	EPA: 1600 DHA: 2400	ONS	Standard Comparator	12 weeks	Safety and efficacy
Chagas et al., 2017	RCT	Mixed Hematological cancers undergoing chemotherapy (n=22)	43.8 + 23.3 y 12M:10F	EPA: 367 DHA: 243	Capsules	Placebo capsules	9 weeks	Nutritional status

Chronic Obstructive Pulmonary Disease								
Calder et al., 2018	RCT [multi-center]	COPD, pre-cachectic and cachectic (n=45)	69.2 ± 6.3 y 45M:55F	EPA: 1600 DHA: 2400	ONS	Standard Comparator	12 weeks	Lean body mass
Ogasawara et al., 2018	RCT [open label]	COPD; hospitalized and rehabilitation during hospitalization (n=45)	77.4 ±9.7 y 41M: 4F	EPA: 1100 DHA: 450	ONS		hospital stay (mean = 12.6 +/- 4.9 d, EPA group, 12.1+/-3.9 d, control group)	Lean body mass
van de Bool et al., 2017	RCT	COPD with low muscle mass undergoing outpatient rehabilitation (n=81)	43–80 y 51% males	EPA: 498-746 DHA: 237-356	ONS	Noncaloric liquid drink	4 months	Body weight, lean body mass, muscle strength

[a]Age reported for the Intervention group

[b]Number of males and females in total reported

Table 2: Outcomes Assessed in Recent Literature

Reference	Biological Measure of Compliance?	Muscle Function?	Muscle Mass? (Method of assessment)	Food Intake?	Measure of Inflammation?
Feijo, Nutrition Journal 2019	X	X	X (BIA)	✓	✓
Akita, Clin Nutr ESPEN 2019	X	X	X (BIA and psoas by CT)	X	x
Aoyama, J Cancer 2019 & Ida, BJS 2017	X	X	X (BIA)	X	x
Haidari, J Diet Suppl 2019	X	X	X (BIA)	X	✓
Hanai, JJCO 2018	X	X	X (Not stated)	X	x
Jantharapattana, Head Neck 2018	X	X	X (BIA)	X	✓
Solis-Martinez, Nutr Ca 2018	X	X	X (BIA)	✓	x
De la Rosa et al, Nutricion Hospitalaria 2019	X	X	X (BIA)	X	✓
Paixao, Nutr J 2017	X	X	X (BIA)	✓	✓
Aredes, Nutrition 2019	X	X	X (unvalidated CT measure of psoas)	✓	x
Laviano, Nutr Cancer 2019	✓	X	✓ (Undescribed DXA and CT)	X	x
Chagas, J Hum Nutr	✓	X	✓	x	✓

Diet 2017			(anthropometrics)		
Calder, J Cachexia, Sarcopenia and Muscle 2018	✓	✓	✓ (DXA)	✓	✓
Ogasawara, Clin Nutr ESPEN 2018	X	X	X (BIA)	x	x
van de Bool, J Cach Sarc Muscle 2017	✓	✓	✓ (DXA)	x	x

X no ✓ yes