**Omega-3 intake and cachexia risk in cancer patients: systematic literature review**

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**ABSTRACT**

**Introduction:** Omega-3 is an essential fatty acid that is needed but the body cannot synthesize it. Omega-3s have good benefits for the body; such as can reduce the production of pro-inflammatory cytokines. Pro-inflammatory cytokines are one of the causes of cachexia in cancer patients. This study wanted to know about the intake of omega-3 either from food or supplements with the incidence of cachexia risk in cancer patients.

**Method:** A systematic literature review search was conducted using Search Engines, such as PubMed, Google Scholar, Science Direct, and DOAJ. The articles identified with the inclusion and exclusion criteria specified in the PICOS table. Then an assessment of the quality of the article was carried out using the JBI Critical Appraisal Tool.

**Result:** From 127 articles, only four studies that eligible to further analysis. In 4 literature studies, three studies used clinical research methods and a retrospective cohort study. Three literature studies show an association between omega-3 supplements with increased body weight, fat mass, and serum albumin. Only one literature study did not show an association between omega-3 supplements with increased body weight, body fat mass, serum albumin, decreased serum CRP or serum IL-6. The forms of omega-3 supplementations consumed by most cancer patients are Fish Oil (FO) and Marine Phospholipids (MPL). FO with a 1-7 grams dose can increase body weight and serum albumin levels in cancer patients. MPL with a dose of 8.5 grams can also increase body weight.

**Conclusion:** This review found varying certainties of evidence of omega-3 supplementation to prevent cachexia. The recommendation for taking FO and MPL supplements is three times a day.

**Keywords:** cachexia, cancer patients, fish oil, omega-3 intake

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**INTRODUCTION**

Cancer is the second leading cause of death in the world. Cancer is a disease characterized by abnormal growth and regulation of growing cells. The incidence of cancer in Indonesia is number 8 in Southeast Asia while ranking 23 in the Asian continent. Based on Riset Kesehatan Dasar (Risksdas) in 2018, the prevalence of cancer in Indonesia has increased from 1.4 per 1000 population to 1.79 per 1000 population.

One of the nutritional problems that need to be considered in cancer patients is cachexia. Cachexia is a metabolic syndrome and a state of malnutrition characterized by unexpected weight loss, loss of body tissue (muscle mass) with or without fat tissue, lack of ability to carry out activities, and changes in metabolism. One of the crucial factors that caused cachexia is the role of various increased cytokines. Proinflammatory cytokines produced by tumor cells that cause cachexia are TNF-α (tumor necrosis factor-alpha), IL-1 ( interleukin-1), IL-6, IFN-γ (interferon-gamma) and STAT3. Cachexia causes patients to feel weak and tired and causes a decrease in quality of life with a prevalence of around 30%. One of the best strategies to overcome cachexia is to regulate nutrient intake and perform physical activity.

A study by Shirai et al. regarding the use of omega-3 supplements to prevent cachexia at a dose of 1.1 grams of EPA and 0.5 grams of DHA in 128 gastrointestinal cancer patients during chemotherapy found significant differences between the control and treatment groups. In the study results, the omega-3 supplement also given affected increasing body fat mass. On the other hand, the research by Hanai et al. gave omega-3 supplements at a dose of 1056 mg of EPA in head and neck cancer patients to prevent cachexia and found no increase in body weight and a reduction in inflammation levels in the body between control and treatment groups.

Based on the description above, omega-3 fatty acids have immunomodulatory properties that reduce the production of pro-inflammatory cytokines. In previous studies, omega-3 EPA and DHA supplements have been used in cachexia. However, evidence supporting these interventions has proven inconsistent. This systematic review aimed to evaluate the current evidence regarding the use of omega-3 intake either from food or supplements with the risk of cachexia among cancer patients.

**MATERIALS AND METHODS**

This systematic literature review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Two reviewers from database inception to the year 2020 to identify relevant articles.
searched the databases Pubmed, Google Scholar, Science Direct, and Directory of Open Access Journal (DOAJ).

**Instrument and Procedures**

The keywords used in this literature search related to patients (patient OR patients); cancer (cancer OR carcinoma OR tumor); cachexia (cachexia OR cachexias); Omega-3 intake (omega 3* food* OR omega 3* supplement* OR omega 3* supplementation* OR omega 3* consumption*). The cancer patient is defined as any cancer with any severity and/or duration. No limitations were placed on cancer sub-population or locations; only English-language articles were included. Outcomes of interest were not specified, allowing for a range of outcomes to be considered. Studies were included if they included any cancer population undergoing any form of conventional cancer treatment. The results used if the data indicate the presence of omega-3 intake in the form of food and supplements, as well as signs of cachexia such as weight loss, loss of body fat mass, increased plasma CRP, increased plasma IL-6, decreased plasma albumin, decreased physical activity, anorexia, and decreased quality of life. Exclusion criteria included data with cancer patients under 18 years or categories of pediatric cancer patients, it cannot be used; the abstract-only publications and any publication identified as already being included in any systematic review seemed eligible for inclusion, thus preventing result duplication.

**Data Analysis**

This study used a hierarchical approach as a first step to assessing the relevance of the research and selecting the research studies to be used. Two reviewers independently screened titles and abstracts first, and then full texts of potentially eligible articles concerning the exclusion criteria, to identify those articles that met full inclusion criteria. The two reviewers then independently abstracted data from each publication using the Joanna Briggs Institute (JBI). The selected literature study was extracted using the JBI Critical Appraisal tool, inclusion and exclusion criteria based on PICOS. The results will be presented in tabular form and analyzed descriptively due to the heterogeneity of the research studies.

**RESULTS**

There were 127 articles initially retrieved. Of the 127 articles, 13 were potentially eligible for inclusion and 114 were then excluded based on title and abstract (Figure 1). At the feasibility study stage, 13 studies were assessed in this stage and identified in full text. Then 9 studies were excluded for a certain reason. In the last stage, namely conformity with the inclusion criteria, 4 selected literature studies were found.

The literature study selected consisted of 274 cancer patients with 4 types of cancer: gastric, head, neck, gastrointestinal, and pancreatic cancer. The age range of the participants was 18 to 80 years. The intervention given is the intake of omega-3 in the form of supplements. This selected literature study showed patients who experienced weight gain, weight loss, loss of body fat mass, increased plasma CRP, increased plasma IL-6, decreased serum albumin, and decreased quality of life. The design method used in the selected study is clinical trial and cohort.

Nemati et al. study used gastric cancer patients undergoing chemotherapy treatment with a vulnerable age of 30 years. Cancer patients with comorbidities will be excluded from this study, and gastric cancer patients used in this study have cancer stages II and III. The patient received omega-3 supplements, 3 times daily for 6 weeks. Supplements given in the form of 1 g of Fish Oil contain 180 mg of EPA and 120 mg of DHA. The method design in this study was a double-blind clinical trial. Anthropometric and laboratory data were collected at the beginning, middle (4 weeks), and end of the study (6 weeks). The outcomes in this study were body weight and serum albumin.

Hanai et al. study used head and neck cancer patients who were undergoing surgical treatment. The inclusion criteria used in this study were the hospital diagnosis stating the patient had head and neck cancer, indications for surgery, having approved the consent form, vulnerable age between 20-80 years, has ECOG performance status with a score of 0-2, weight loss 5% in 6 months, life expectancy ≥ 6 months, and the patient still has good main organ function. While the inclusion criteria in this study were patients who had digestive tract disorders so that they could not receive oral or enteral intake, a combination of organ disorders, infection before surgery, had heart, liver, kidney disease, diabetes mellitus, and hyperlipidemia. Then patients who take steroid drugs, have previously taken EPA supplements, have allergies to Prosure components, pregnant women, and breastfeeding mothers will also be excluded from this study. Prosure oral nutritional supplements were administered for 14 days before surgery and 14 days after surgery. In the study of Hanai et al., anthropometric measurements such as body weight and body fat mass were carried out before the study, the day before surgery, 7 days after surgery, and 14 days after surgery. Measurements of laboratory data such as serum albumin and serum CRP were performed on the day of surgery, day 1, day 3, day 7, and day 14 after surgery. However, the measurement of serum IL-6 was only done twice before the study and 14 days after surgery. The patient was given the oral nutritional supplement Prosure (240 ml) 2 times a day. The method design in this study was a double-blind clinical trial. The outcomes in this study were body weight, body fat mass, serum albumin, serum CRP, and serum IL-6.

Shirai et al. study used gastrointestinal cancer patients undergoing chemotherapy treatment, where these gastrointestinal cancers consisted of esophageal, gastric, colon, bile duct, and pancreatic cancer. The inclusion criteria in this study were all patients who had been diagnosed with gastrointestinal cancer from the responsible institution, aged between 18-80 years, experienced 5% weight loss, had a life expectancy of 3 months, and Karnofsky performance status with a score of 70 or more. Measurement of serum CRP and body fat mass was carried out when the patient visited the hospital every 3 months. Patients were given FO supplements with a consumption time of 1 or 2 times a day, each FO supplement contains 16 g protein,
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1.1 g EPA, 0.5 g DHA, and 355 calories. The design method in this research is a retrospective cohort study. The outcomes in this study were serum CRP and body fat mass.

Werner et al. research used pancreatic cancer patients with inclusion criteria such as at least 18 years of age, the patient's life expectancy is 3 months, 5% weight loss since diagnosis, Karnofsky performance status with a score of 60%, no allergies to fish or seafood, nutritional intake through oral, no blood clotting disease and psychological disease. There were 60 patients according to the inclusion criteria and they chose Fish Oil (FO) or Marine Phospholipids (MPL) supplements randomly to be taken 3 times a day a week.

The FO supplement contains 60% FO and 40% Medium Chain Triglycerides consisting of 6.9 g/100 g EPA and 13.6/100 g DHA. While MPL contains 35% omega-3 phospholipids and 65% natural fat consisting of 8.5 g/100 g EPA and 12.3 g/100 g DHA. Changes in body weight will be reported by the patient every day (self-reported) and body fat mass measurement using skinfold thickness where measurements are made in 3 parts of the body, namely the upper arm, forearm and waist (iliac). While the questionnaires to assess the quality of life of patients used were EORTC-QLQ-C30 (quality of life questionnaire for cancer patients) and PAN26 (quality of life questionnaire for pancreatic cancer patients). The method design in this study was a double-blind controlled trial. The outcome of this study is the patient's weight and quality of life.

DISSCUSSION

This review investigated omega-3 to prevent cachexia in adult cancer patients. Moderate certainty of the evidence was found for the beneficial effects of omega 3 intakes to prevent cachexia. The studies showed unequal outcomes due to differences in the use of cancer types, medical treatment, patient age, omega-3 supplements, supplement dosage and research methods.

Nemati et al. study report stated that omega-3 supplements could increase body weight and serum albumin in gastric cancer patients undergoing chemotherapy. Another study by Hanai et al. research report stated different results that omega-3 supplements can not increase body weight, cannot increase body fat mass, cannot increase albumin, cannot decrease serum CRP values and cannot decrease serum IL-6 in head and neck cancer patients undergoing surgical treatment. There was no relationship between omega-3 supplements with some of these indicators, possibly due to medical complications in patients after surgery and dysphagia.

This study's results align with a study by Schmidt, which stated that omega-3 supplements given to the intervention group did not show any changes in laboratory data, increased body weight, and had no side effects. The supplement dose given was 4.8 grams/day and patient compliance was 96.4%. This shows that although the patient's compliance is high, it still does not show any changes in their condition.

In the study of Shirai et al., it was stated that there was no relationship between omega-3 supplements and a decrease in serum CRP, but there was a relationship between omega-3 supplements and increased body fat mass in gastrointestinal cancer patients undergoing chemotherapy treatment. This study also correlated gender, age of cancer patients, type of gastrointestinal cancer, classification of gastrointestinal cancer, serum CRP, serum albumin, and omega-3 supplements to chemotherapy tolerance and clinical factors. But the results show that only the age of cancer patients and serum CRP are related, if the age is getting younger and the serum CRP has a high value, the tolerance to chemotherapy is getting worse.

In addition, this study also discusses the impact of omega-3 supplements on patient survival for the next 6 months. The impact of FO supplementation was analyzed using Kaplan-Meier and mGPS 1 or 2. An mGPS 1 or 2 rating was obtained from high serum CRP values (> 0.5 mg/dL) or low albumin values (< 3.5 g/dL). Kaplan Meier's analysis showed that there was no significant difference between the survival of patients who were given FO supplements and patients without FO supplements. But the analysis of mGPS 1 or 2 showed a significant difference where the prognosis of patients who were given FO supplements was better than those without.

The research of Werner et al. stated that Fish Oil (FO) and Marine Phospholipids (MPL) supplements could maintain body weight in pancreatic cancer patients. The researchers hypothesized that MPL supplements with higher doses...
could stabilize body weight more than FO supplements with lower doses. FO supplements have a lower dose but contain Medium Chain Triglycerides (MCT) of about 200 mg per capsule. This MCT has good solubility and fast absorption in the intestine, which is why low-dose FO supplements can still stabilize body weight. Although FO supplements can stabilize body weight, MPL supplements are more acceptable to pancreatic patients because FO supplements have gastrointestinal side effects such as loss of taste (taste), nausea, and flatulence. This study also stated that there was no relationship between FO and MPL supplements on the quality of life of pancreatic cancer patients.9

This study’s results differ from Taylor’s research, which stated that low-dose MPL could increase body weight. Cancer patients consume MPL at a dose of 1.5 grams/day. MPL consumption was carried out for 6 weeks, and this study also measured patient compliance, appetite, quality of life, fatty acid profile, and blood cells. The results showed that although low-dose MPL increased by 0.6% weight gain, appetite and quality of life improved for 6 weeks.11 Weight gain in cancer patients with cachexia is very important because if the body weight increases and the patient’s nutritional status reaches normal values, the life expectancy of cancer patients can be longer. In addition, an increase in serum albumin in cancer patients is also important because a decrease in serum albumin values indicates cancer patients er in a state of malnutrition and inflammation. If there is a decrease in the value of serum albumin, it can cause an increase in the need for amino acids, if the amount is limited from food intake, the amino acids will be obtained from the breakdown of skeletal muscle protein. The breakdown of amino acids from skeletal muscle protein causes changes in muscle mass so that patients will experience a decrease in muscle strength, resulting in progressive muscle dysfunction.12

Then a decrease in fat mass, if it occurs continuously, indicates that fat stores in the body have been converted into energy so that free fatty acids are carried to the liver to be converted into glucose. Lipotrophic factors produced by some tumors also cause fat breakdown (lipolysis), elevated serum lipid levels and hyperlipidemia. In the end, cancer patients will release the proinflammatory cytokine TNF (Tumor Necrosis Factor), which inhibits the action of free lipoprotein enzymes, where this inhibition causes fat storage depletion, serum hyperlipidemia, and decreased body fat mass.14

One of the serums that indicate high inflammation in the body is C-Reactive Protein (CRP) and serum IL-6. CRP is one of the acute phase proteins, which indicates that if CRP increases and does not decrease, the body’s response to inflammation is still high.14 Generally, cancer patients have a low immune system so they are easily exposed to infections which results in high serum CRP values.15 Meanwhile, serum IL-6 is an important mediator in the mechanism of the immune system through immune system regulation. If the serum IL-6 concentration increases, it will cause impaired iron use, suppression of erythrocytes, inadequate erythropoietin production, and shortening of red blood cells.16 If serum CRP and serum IL-6 each show an increase, it can be concluded that inflammation in the body is still high and the body’s immune system has decreased.

The results of a systematic literature review that has been carried out on the 4 literature studies above show the relationship of omega-3 supplements in the form of Fish Oil (FO) with a dose of 1-7 grams can increase body weight and serum albumin levels. While omega-3 supplements in other forms, namely Marine Phospholipids (MPL) at a dose of 8.5 grams can also increase body weight. The recommendation for consuming FO and MPL supplements is 3 times a day.

In summary, this review found varying certainties of evidence of omega-3 supplementation to prevent cachexia. FO supplements where every 1 gram contains 180 mg of EPA and 120 mg of DHA can increase body weight and increase serum albumin in gastric cancer patients during chemotherapy. Omega-3 supplements in the form of Prosure containing 1056 mg of EPA could not increase body weight, body fat mass, serum albumin, serum CRP and serum IL-6 in head and neck cancer patients during surgery. FO supplements containing 16 g protein, 1.1 g EPA, 0.5 g DHA, and 355 kcal could not decrease serum CRP values but could increase body fat mass in gastrointestinal cancer patients during chemotherapy. FO supplement containing 60% FO and 40% MCT (6.9 g/100 g EPA and 13.6 g/100 g DHA) and MPL supplement containing 35% phospholipids and 65% natural fat (8.5 g/100 g EPA and 12.3 g/100 g DHA) stabilized body weight but did not show an association with the patient’s quality of life. Supplements (FO) with a dose of 1-7 grams can increase body weight and serum albumin levels. While omega-3 supplements in other forms, namely Marine Phospholipids (MPL) at a dose of 8.5 grams can also increase body weight. The recommendation for consuming FO and MPL supplements is 3 times a day. Higher quality research is warranted to help guide clinical practice and increase evidence certainty.

**CONCLUSIONS**

**ETHICAL CONSIDERATION**

Not applicable.

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The author declares that there is no conflict of interest.

**AUTHOR CONTRIBUTION**

All authors similarly contribute to the investigate concepts, information
acquisitions, information investigation, and factual investigations, changing the paper until the consideration is detailed through publication.

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