Meta-analyses

A systematic review and meta-analysis of the n-3 polyunsaturated fatty acids effects on inflammatory markers in colorectal cancer

Michel C. Mocellin [a], Carolina Q. Camargo [a], Everson Araujo Nunes [b],
Giovanna M.R. Fiates [a], Erasmo B.S.M. Trindade [a, *]

[a] Department of Nutrition, Graduate Program in Nutrition, Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil
[b] Departament of Physiology, Laboratory of Investigation in Chronic Diseases, Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil

ARTICLE INFO

SUMMARY

Background: Cancer and inflammation are closely related and an exacerbated inflammatory process can lead to tumor progression and a worse prognosis for the patient with cancer. Scientific literature has shown evidence that n-3 polyunsaturated fatty acids (PUFA) have anti-inflammatory action, and for this reason could be useful as an adjuvant in the treatment of some cancers.
Objective: A systematic review and meta-analysis of the literature was conducted until September, 2014, to evaluate the effects of n-3 PUFA on inflammatory mediators in colorectal cancer (CRC) patients.
Patients and methods: Clinical trials were systematically searched in three electronic databases and screening reference lists. Random meta-analysis model was used to calculate the overall and stratified effect sizes.
Results: Nine trials, representing 475 patients with CRC, evaluated effects of n-3 PUFA on cytokines ($n = 6$) and/or acute phase proteins ($n = 5$) levels. n-3 PUFA reduce the levels of IL-6 (SMD -2.34; 95% CI -4.37, -0.31; $p = 0.024$) and increase albumin (SMD 0.31; 95% CI 0.06, 0.56; $p = 0.014$) in overall analyses. In stratified analyses, reduction in IL-6 levels occurs in surgical patients that received 0.2 g/kg of fish oil parenterally at postoperative period (SMD -0.65; 95% CI -1.06, -0.24; $p = 0.002$), while, increase in albumin concentration occurs in surgical patients that received ≥ 2.5 g/d of EPA + DHA orally at preoperative period (SMD 0.34; 95% CI 0.02, 0.66; $p = 0.038$). In patients undergoing chemotherapy, the supplementation of 0.6 g/d of EPA + DHA during 9 week reduces CRP levels (SMD -0.95; 95% CI -1.73, -0.17; $p = 0.017$), and CRP/albumin ratio (SMD -0.95; 95% CI -1.73, -0.18; $p = 0.016$).
Conclusions: The results suggest benefits on some inflammatory mediators with the use of n-3 PUFA on CRC patients, but these benefits are specific to certain supplementation protocols involving duration, dose and route of administration, and also, the concomitant anti-cancer treatment adopted.

1. Introduction

Independently of the origin of the tumorigenesis process, many cancers share a common mechanism characterized by a generalized immunosuppression and the activation of pro-inflammatory cell signaling, which promotes progression, survival, proliferation, invasion, angiogenesis and systemic spread of the tumor tissue [1]. The participation of inflammatory mediators, as cytokines and chemokines, have a key role in this course by orchestrating the anti-cancer defense line (IL-12, Interferon − IFN) or by acting such as protumorigenic agents (IL-1, IL-6, IL-17, TNF) [2]. These inflammatory molecules are produced by immune, cancer and stroma cells through the activation of various transcription factors, such as Nuclear Factor Kappa B (NF-kB), Activator Protein-1 (AP-1), Signal Transducers and Activators of Transcription 3 (STAT3), and Smad. For details about the interaction among these cells and the role of specific cytokines and chemokines on anti or protumorigenic mechanisms in tumor microenvironment, see important reviews about the theme [2−6].

In the established tumors, the balance among inflammatory factors is profoundly tilted toward pro-tumor inflammation. Without therapeutic intervention (anti-cancer treatment),

* Corresponding author. Graduate Program in Nutrition, Department of Nutrition, Health Science Center, Federal University of Santa Catarina, Reitor João David Ferreira Lima Campus, Trindade, Florianópolis, Santa Catarina, Zip Code: 88040-900, Brazil. Tel.: +55 48 3721 9784; fax: +55 48 3721 9542.
E-mail address: erasmotrindade@gmail.com (E.B.S.M. Trindade).

advanced tumors rarely regress [3,6]. Additionally, chemotherapy and radiation also activate inflammatory pathways, which subsequently can contribute to the chronic inflammation related to cancer [2]. Other repercussions caused by these procedures include chemo and radiation resistance, poor metabolism of cytotoxic anti-cancer drugs with the increase of toxic symptoms and progressive weight loss, which leads to a worse prognosis represented by the increased malignancy and low survival, and poorer quality of life [7].

Due to its impact on the course of the disease, the treatment of cancer should involve therapies targeting at inhibiting and/or resolving the chronic inflammation. Within this perspective, many studies have reported several benefits with the use of the n-3 polyunsaturated fatty acids — PUFA (eicosapentaenoic and/or docosahexaenoic acid, EPA or DHA) to cancer patients, assigning a possible action of these fatty acids for the inhibition and resolving of the inflammation, and based on that, the use of these fatty acids to support cancer treatment [8—12] (For understanding the action of n-3 PUFA on inflammation see [13—15]).

In the last years, some systematic reviews of the literature were performed in order to gather evidence and verify the efficacy of n-3 PUFA in altering the concentration of inflammatory mediators/markers in different clinical situations. There is some inconclusive evidence, that n-3 PUFA decreases the concentrations of inflammatory mediators/markers in: chronic heart failure; pancreatitis; chronic renal disease; critical illness (sepsis); and, Alzheimer's disease [16,17]. In cardiovascular disease, the results of studies are controversial and inconclusive, while in healthy subjects, the evidence suggests that there is not reduction in the inflammation with the use of n-3 PUFA [17,18].

Thus, this meta-analysis was conducted in order to verify the action of the n-3 PUFA (Intervention) on different inflammatory mediators (cytokines and acute phase proteins) (Outcomes) in colorectal cancer patients (Population), which is one of the five main types of cancer responsible for the death of people worldwide, besides being a clinical model of tumor that present a close association with inflammation [19]. Secondary objectives include verify if some clinical variables of the study patients as well as, if some supplementation protocol characteristics may influence the anti-inflammatory action of n-3 PUFA.

2. Methods

The method of this systematic review and meta-analysis was prepared in accordance with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [20].

2.1. Search strategy

Systematic research of trials published until September, 2014 was conducted on MEDLINE (via PubMed; National Library of Medicine, Bethesda, Maryland), Science Direct (via Scopus, Elsevier, Philadelphia, USA) and Web of Knowledge (via Web of Science, Thomson Reuters, New York, USA) using the combination of the categories of search terms shown in Table 1.

The search was elaborated according to PICO strategy considering: Patients/population: colorectal cancer patients; Intervention: n-3 PUFA; Comparisons: parallel group did not receive n-n-3 PUFA as intervention; and, Outcomes: cytokines and acute phase proteins. The search in databases was done using Boolean operators (OR and AND), parentheses, quotation marks and asterisks. Quotation marks were used to search for exact terms or expressions; parentheses were used to indicate a group of search terms or combine two or more groups of search terms enabling all possible combinations of sentences; asterisks (*) or cipher symbol ($) were used to search all words derived of the precedent inflected part. Any filters to refine search were not added. Additionally, reference lists of all identified studies and important reviews about the theme were hand-searched for relevant trials.

The searches were conducted in the online database and the results exported to the reference manager software EndNote® version X7 (Thomson Reuters, New York, USA).

2.2. Selection criteria

Titles and abstracts of the articles, and when clear information was not presented, the full text, were reviewed in order to choose those which were eligible. The eligibility criteria were: controlled or randomized clinical trials performed in humans; use of n-3 polyunsaturated fatty acids as intervention, isolated or added in dietary formulas or as lipid emulsion; sample composed of subjects with over 18 years of age and, only affected by malignant colorectal neoplasm; and those trials that had assessed the cytokines or acute phase proteins levels in vivo.

Trials that did not meet the inclusion criteria, duplicated or triplicated publications from the same trial, as well as, trials that were originally published in languages other than English, Spanish or Portuguese, were excluded.

2.3. Data extraction

Data were extracted from eligible articles independently by two reviewers and cross-checked. Articles were consulted again in case of divergence of opinions. For qualitative synthesis, the following data were extracted: locality, methodological characteristics (study design, blinding, randomization technique), patient characteristics (mean age, Body Mass Index -BMI, cancer stage), sample size enrolled, anti-cancer treatment adopted, intervention characteristics (formulation, dose, duration of supplementation and route of administration), and, proportion of loss to follow-up. Outcomes data extracted were mean and standard deviation of the inflammatory mediators/markers (cytokines and acute phase proteins). For the presentation of results, we consider the biomarker concentration at the final moment of supplementation or at any other moment during the supplementation period, which could be significantly lower or higher than control.

Quantitative analysis of the selected trials was performed for interleukins 6 and 1β (pg/mL), tumor necrosis factor — TNF (pg/mL), C-reactive protein — CRP (mg/L), albumin (g/dL) and CRP/Albumin ratio (inflammatory and nutritional risk of complications [21]). For

Table 1
Groups of search terms (PICO strategy) used for search strategy.

PICO's criteria	Descriptions and search terms used for each criteria
Patient/population	Patients with colorectal cancer ((cancer OR neoplasm OR tumor) AND (colorectal OR colon OR rectal))
Intervention	n-3 polyunsaturated fatty acids (EPA and DHA) ("fish oil" OR "n-3 polyunsaturated fatty acids" OR "Omega-3" OR "eicosapentaenoic acid" OR EPA OR "docosahexaenoic acid" OR DHA OR "linolenic acid" OR "polyunsaturated fatty acids" OR Immunonutrition)
Comparisons	Parallel group did not receive n-3 polyunsaturated fatty acids ("controlled clinical trial" OR "randomized clinical trial")
Outcomes	Inflammatory markers (cytokines and acute phase proteins) (cytokine OR interleukin OR "C-reactive protein" OR CRP OR "tumor necrosis factor" OR TNF OR albumin OR "inflammatory markers" OR inflammation OR "acute phase protein")