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Association among antioxidant nutrients intake, nutritional status and side effects of cancer patients undergoing antineoplastic treatment

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ABSTRACT

Objective: To analyze the influence of antioxidant nutrients consumption over the nutritional status of cancer patients as well as over the occurrence of side effects during antineoplastic treatment.

Methods: This is a cross-sectional study carried out at a philanthropic hospital in northeastern Brazil with cancer patients undergoing antineoplastic treatment, aged ≥ 18, of both genders. Sociodemographic, clinical and anthropometric data were collected, as well as the record of symptoms related to the adverse effects of antineoplastic treatment. The data on the consumption of food sources of antioxidant nutrients (vitamin A, C, and E, zinc, and selenium) were estimated through Food Frequency Questionnaires (FFQ) adapted from Mannato (2013), including foods consumed in the region, and evaluated according to the nutritional recommendations of the Institute of Medicine (2001).

Results: This sample consisted of 42 participants, 76.2% female and with a mean age of 53. Breast cancer was the most frequent cancer type (52.4%), and 47.6% of cases were metastatic. Regarding nutritional status, 57.2% of patients were overweight or obese, and 38% reported significant weight loss. Vitamin A and C intake were adequate in 92.85% and 76.19% of patients, respectively, but vitamin E, zinc and selenium ingestion all showed low adequacy.

Conclusion: No correlation was found between antioxidant micronutrient intake, nutritional status, and side effect frequency in oncologic patients undergoing treatment. This underscores the complexity of cancer biology, emphasizing the need for continuous, individualized nutritional support with tailored interventions for cancer patients.

KEYWORDS

Oxidative Stress. Immunonutrition Diet. Nutritional Status. Micronutrients.

INTRODUCTION

Cancer is the outcome of a rapid and disorganized cellular growth, which can expand to other body structures and result in metastasis[1]. Nowadays it is considered one of the main public health problems, with an increasingly high incidence and mortality all over the world. In Brazil, according to the National Institute of Cancer (INCA) - Estimate 2023-2025 - data, 704,000 new cancer cases are expected[2].

Amongst the disease's modifiable factors, nutrition plays an important role, not only in carcinogenesis itself, but also in it's progression[3]. It is thought that a third of all cancer-related deaths occur due to behavioral and nutritional related risks, such as sedentarism, obesity, abusive alcohol and tobacco use and low consumption of fruits, legumes and vegetables[4]. For instance, in Brazil, approximately 5% cancer cases and 7% cancer-related deaths can be attributed to an inadequate nutrition[5].

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Cancer's intrinsic demands, as well as the toxicity of it's treatment, can culminate in increased reactive oxygen species (ROS) formation and in an elevated oxidative stress, which tend to damage molecules such as deoxyribonucleic acid (DNA), ribonucleic acid (RNA), lipids and proteins, consequently leading to an increased need for antioxidant nutrients ingestion[6,7]. Therefore, a diet with a high antioxidant capacity could provide protective effects against cancer, favorably affecting antineoplastic treatment, given that this dietary profile has been linked to a decrease in DNA damage and an increase in apoptosis induction, immunologic response and activation of tumor suppressor genes expression[8,7].

The benefits of consuming fruits and vegetables, specifically for oncologic patients, occur primarily due to being important sources of antioxidant vitamins and minerals (such as vitamins A, C and E, selenium, zinc and copper) and to containing low-calorie-density and high concentrations of dietary fiber, besides it's consumption being frequently associated with a lower intake of ultraprocessed foods[9,10].

Deficiency of antioxidant micronutrients can be a common theme in these patients, not only during diagnosis, but also during treatment[6]. Initially, it had been believed that this inadequate ingestion would have repercussions on the immune system, increasing toxicity and negatively affecting treatment[7]. Nevertheless, it has been currently reported that antioxidant compounds may not induce as much benefits during antineoplastic treatment as previously thought, due to not offering adequate protection against oxidative stress and for inducing chemoresistance, consequently leading to unfavorable prognoses[11,12]. Despite the importance of an adequate intake of antioxidant micronutrients by cancer patients, only few studies address the influence of antioxidants over adverse effects experienced during chemotherapy.

Cancer and antineoplastic treatment can cause adverse effects that interfere with patients' nutritional status, eating behaviors and, consequently, quality of life. In this context, protein-calorie malnutrition occurs due to the metabolic alterations associated with the oncologic process, contributing to an increased rate of proteolysis, lipolysis and gluconeogenesis, which are closely linked to the expected disturbance in basal metabolic rate as well as to the loss of adipose tissue and muscle mass[13].

Thereby, the aim of this study is to identify the association among antioxidant nutrients consumption, anthropometric evaluation and the occurrence of adverse effects in cancer patients undergoing antineoplastic treatment, in order to establish factors that may possibly impact their quality of life and nutritional management.

METHODS

This is a cross-sectional study with a non-probabilistic sampling design by convenience, carried out at the Nutritional Outpatient of the Integral Medicine Institute Professor Fernando Figueira (IMIP) in the Brazilian state of Pernambuco, during March through July 2023.

The population in this study was composed of cancer patients undergoing antineoplastic treatment (chemotherapy and/or radiotherapy). The adopted inclusion criteria were: patients diagnosed with any type of malignant neoplasm undergoing antineoplastic treatment for at least a month or that had gone through a full cycle of treatment, ≥ 18 years old, of both genders. Were excluded from this study patients who had just began treatment, since those are unlikely to have yet experienced adverse effects from antineoplastic therapy; patients who had previously been submitted to any medium or large surgical procedure; pregnant, postpartum or lactating women; patients suffering from any cognitive deficit or major psychiatric dysfunction that may impair the ability to provide the necessary information to fill the instruments of research and/or anthropometry.

To characterize the population, variables such as sociodemographic (sex, marital status, schooling and income), disease status (diagnosis, time since diagnosis, treatment type and duration, clinical staging - I, II, III and IV, metastasis and other associated diseases) anthropometric (weight, height, body mass index and percentage of weight loss), lifestyle and eating patterns were collected.

The data on food consumption, especially sources of vitamins A, C, and E, as well as zinc and selenium, were estimated through Food Frequency Questionnaires (FFQ), adapted from Mannato (2013)[14], with the inclusion of foods consumed in the study region. No FFQ validated for the oncological population was found in the literature, so the FFQ developed for the general population was used. During the FFQ completion, participants were instructed to report the average frequency of consumption of a particular food per day, week, month, and year, as well as the portion sizes of the foods consumed throughout the antineoplastic therapy. The obtained data were individually compared to the current nutritional recommendations (IOM, 2000; 2001)[15].

The Brazilian Table of Food Composition (TACO®) was used in order to estimate the amount of each nutrient consumed. The consumption of dietary supplements was evaluated separately. Since only 3 patients used supplements for less than one week, this consumption was not considered in the estimation of intake, as the amount was not sufficient to significantly impact the observed outcomes. Reports of adverse symptoms were collected through authorial questionnaire that assessed the presence of constipation, diarrhea, dysphagia, dyspepsia, xerostomia, nausea, changes in smell, dysgeusia, vomiting, gastritis and mucositis. The degrees of severity of each gastrointestinal disorder were adapted to Portuguese based on the Common Terminology Criteria for Adverse Event *(CTCAE)*, in which: Grade I, when manifested

in a light manner, infrequently and solved without the need of medical intervention; Grade II, when manifested in a moderate manner, frequently and solved with the need of very local or non invasive medical intervention; Grade III, when manifested in a severe manner, having needed hospitalization or previous prolonged internment and with limiting self-care.

SigmaStat 3.5 (*Systat Software*®, EUA) was used for the statistical analysis. For all analyses, significance level was set to 5%. The *Kolmogorov Smirnov* test was applied to test the normalcy of the distribution of the obtained data. Variables were presented as mean value and standard deviation or as median value and minimum and maximum, according to it's distribution. Either *Student's t test* or *Mann-Whitney's U test* were used for the comparison between groups.

For the association analysis of the categorical variables contained in the CTCAE questionnaire, *Fisher's test* was used. *Pearson's Correlation test* was used for the normal distribution variables, while *Spearman's Correlation test* was used for the non-normal distribution variables. In order to rate the degree of relation between variables, metrics were adopted for the coefficients. Thus, $r < 0.4$ (weak correlation); $r \geq 0.4$ and < 0.6 (moderate correlation); $r \geq 0.6$ (strong correlation).

This study was approved by the Ethics Committee of the Integral Medicine Institute Professor Fernando Figueira - IMIP/PE, CAAE: no 66891623,3.0000,5201, approval no 6,148,382. All participants were informed about the objectives and procedures, and signed both copies of the Free and Informed Consent Term (TCLE).

RESULTS

The sample was composed of 42 participants, 76.2% (n=32) of whom were females, while 23.8% (n=10) were males. Most participants were adults (69%), and 31% were elderly. Mean age of the sample was 53 years old (±13.5). In regards to lifestyle habits, most patients denied alcohol and tobacco use, and only 14.3% (n=6) reported physical activity practice. As for socioeconomical data, most participants (85.7%) reported a family income of between 1 to 2 minimum wages, 28.6% lived out of the state's capital and 9.5% were illiterate.

While on the subject of oncologic diagnosis, breast cancer was the most frequent type (52.4%), followed by uterine, prostate, Kaposi's Sarcoma and bladder, which were clustered in the same group (31%), and gastrointestinal cancers (16.7%). A predominance of late stage cancers was observed, of which 47.6% were metastatic. Regarding the antineoplastic treatment, 88.1% of participants were exclusively undergoing chemotherapy. In the manner of emetogenicity of the chemotherapy, 54.76% of the administered medication had moderate to high emetogenic effect, meaning that 30% to 90% of patients would experience emetic episodes during treatment. Most participants (69%) reported suffering from some type of comorbidity, including hypertension, diabetes, dyslipidemia and fatty liver disease.

When assessing nutritional status via Body Mass Index (BMI), 57.2% of the sample could be classified as overweight or obese (n=24), while 11.9% showed some degree of malnutrition (n=5). Mean BMI was 27.24kg/m² (±6.1). Moreover, approximately 38% (n=16) of patients had had significant weight loss since the beginning of diagnosis, with an average time since diagnosis of 6 months (range of 3 to 13 months) and an average treatment time of 4 months (range of 2 to 6 months). Data on anthropometric assessment and diagnosis time are expressed in table 1.

For the purpose of identifying an association between time since diagnosis and anthropometric data, the sample was divided into two groups: one whose patients had less than 6 months since diagnosis and the other whose patients had more than 6 months since diagnosis. Both groups presented no significant difference in regards to BMI and rate of weight loss. Data is expressed in table 2.

Table 1. Characterization of anthropometric variables relative to the cancer patients undergoing antineoplastic therapy

Anthropometric data	Mean/Median	SD/IQR* (25-75)
Usual weight (kg):	71.00	62.75-89.85
Current weight (kg)	70.37	17.46
BMI (kg/m2):	27.24	6.09
Weight loss%	-6.04	11.5
Time since diagnosis months)	4.00	3.00-13.00

*Interquartile range; n = sample number; % = sample proportion; BMI = Body Weight Index.

Table 2. Association among time since diagnosis, nutritional status and weight loss of cancer patients undergoing antineoplastic treatment.

Variables	Time since cancer diagnosis		*p
	<6 months	≥6 months	
	Mean (SD)	Mean (SD)	
BMI	28.38 (7.32)	26.38 (4.98)	0.298
WL(%)*	-4.55 (10.16)	-7.15 (12.56)	0.478

*T student's test; *Weigh loss %.

After evaluating the intake of vitamin A and C through frequency of consumption of the vitamin's main food sources, and comparing it to the Recommended Dietary Allowance (RDA), based on the Dietary Reference Intakes (DRIs), it was established that 92.85% and 76.19% of participants had adequate ingestion, respectively. In contrast, the intake of vitamin E, zinc and selenium showed low adequacy, with only 2.38%, 4.76% and 38.09% of participants having adequate consumption of these nutrients, respectively.

While evaluating the median nutrient intake of the sample and comparing it to the Estimated Average Requirement (EAR), standardized for group evaluation, an inadequacy for vitamin E (41.70%) and zinc (51.85%) was established. As for the other nutrients assessed, median intake was adequate based on the EAR values. Micronutrient intake of the oncologic group undergoing antineoplastic treatment expressed in table 3.

According to the *Common Terminology Criteria for Adverse Effect*, the symptoms conferred 2nd and 3rd degree of severity, i.e. which had required some type of medical intervention or even hospitalization, were constipation (26.19%), diarrhea (19.04%), nausea (23.80%) and vomiting (9.52%)

Table 3. Micronutrient intake of the oncologic group undergoing antineoplastic treatment

Micronutrients	Median	IQR
Vitamin A (mcg/day)	1394.00	1051.00-2227.00
Vitamin C (mg/day)	182.00	73.30-378.00
Vitamin E (mg/day)	5.92	4.11-7.88
Zinc (mg/day)	3.63	2.79-4.89
Selenium (mcg/day)	41.50	32.10-58.40

In order to verify the potential existence of an association between antioxidant nutrients intake and display of side effects, patients were divided into two groups: one whose participants reported experiencing less than three distinct side effects and the other one whose participants reported experiencing more than three distinct side effects. No association was observed between the amount of reported side effects and antioxidant nutrients intake. In addition, there was no correlation between the percentage of weight loss and BMI in relation to mean/median of antioxidant nutrients dietary consumption. Data are expressed in Table 4.

Table 4. Comparison among the micronutrients intake of the cancer patients undergoing antineoplastic treatment

	No. of side effects			Weight loss %		BMI	
	<3 Med (IQ)	≥3 Med (IQ)	p[a]	Rho	p[b]	Rho	p[b]
Vit A							
mcg/day	1794 (992-2526)	1394 (1056-2106)	0,539	0.171	0.279	0.030	0.851
adequacy%	334 (180-399)	199 (151-301)	0.137	0.192	0.223	0.007	0.966
Vit C							
mg/ day	166 (139-319)	201 (74.0-378)	0.741	-0.053	0.740	0.155	0.324
adequacy%	222 (185-426)	269 (98.7-504)	0.746	-0.053	0.740	0.155	0.324
Vit E							
mg/ day	6.70 (3.38-7.38)	5.29 (4.15-8.14)	0.626	0.286	0.067	0.086	0.589
adequacy%	44.7 (22.5-49.2)	35.3 (27.7-54.2)	0.578	0.286	0.067	0.086	0.589
Zinc							
mg/ day	3.41 (3.21-4.40)	3.66 (2.63-5.19)	0.789	0.133	0.401	0.105	0.506
adequacy%	42.7 (40.1-55.0)	45.7 (32.9-64.8)	0.596	0.133	0.401	0.105	0.506
Selenium							
mcg/ day	48.8 (39.2-56.5)	38.2 (31.9-58.7)	0.560	-0.021	0.894	0.079	0.618
adequacy%	88.7 (71.3-103)	69.4 (58.0-107)	0.878	-0.021	0.894	0.079	0.618

DISCUSSION

The anthropometric assessment revealed a high prevalence of overweight and obesity in the present sample. Bossi et al. (2021)[16], in a review of observational and clinical studies that assessed nutritional characteristics of patients, focusing on factors like BMI, dietary ingestion and the presence of comorbidities, also found a high prevalence of overweight and obesity among oncologic patients, emphasizing that these indexes are frequently observed in many different types of cancer. The authors claim that obesity may impact the disease's progression and the treatment's outcome. Besides, Arends (2024)[17] also highlights the complexity of the nutritional status in cancer patients, with overweight and obesity being relevant concerns during nutritional management.

In a systematic review developed by Salas et al (2022)[18], containing data of 150 meta-analyses, cluster analyses or intervention trials, as well as of 93 cohort studies, the presence of obesity in women with non metastatic breast cancer was associated with a higher risk of secondary cancer and a higher all cause and cancer-specific mortality. Overweight and obesity in these patients were probably associated with a higher risk of cancer recurrence.

The significant rate of weight loss observed in the present study corroborates with the findings of Arends (2024)[17], who found, while in a systematic approach to identify and analyze studies addressing causes, consequences and options of treatment for malnutrition, that this condition may be influenced by several factors, including cancer type and stage, side effects of treatments (such as chemotherapy and radiotherapy), as well as associated comorbidities, which were relevant factors also found in the present study. Additionally, Meza-Valderrama et al. (2021)[13], while evaluating sarcopenia and cachexia, concluded that their high prevalence among cancer patients negatively impacts quality of life and prognosis.

In the present study, although the majority of the sample was classified as having no nutritional impairment according to Body Mass Index (BMI) — with 57.2% of patients presenting as eutrophic, overweight, or obese, and only 11.9% showing some degree of malnutrition — significant weight loss was observed in approximately 38% of participants over the past six months. A similar result was found in a previous study conducted by our research group, which evaluated a comparable oncologic population hospitalized in the same clinic, where 78.8% of patients experienced significant weight loss in the preceding six months despite a low prevalence of malnutrition according to BMI[19]. These findings suggest that BMI alone may not adequately reflect nutritional risk in cancer patients, especially in the presence of recent weight loss, highlighting the need for a more comprehensive nutritional assessment.

Although the intake of vitamin A and C in the present sample was adequate, the low adequacy of vitamin E, zinc and selenium implicates in a nutritional vulnerability that may affect patient's immunologic system and recovery. This result is consistent with the observations made by Skrajnowska e Bobrowska-Korczak (2019)[20], who emphasized the importance of zinc in immunologic defense and it's role during oncologic treatment. It's deficiency could be associated with a higher susceptibility to infections and could compromise the efficacy of the cancer therapy Despite that, the high proportion of patients presenting adequacy for vitamin A intake is very significant, seeing that it is associated with a higher protection against the development of cancer and a maintenance of immunologic functions. Thus, this adequacy can contribute to the efficacy of the oncologic treatment and to an improvement on quality of life, as discussed in a study done by Doldo et al. (2015)[21]. Nonetheless, according to Salas et al (2022)[18], supplementation with high doses of antioxidants were seen to repair the oxidative damage induced by the treatment against cancer cells, thus limiting the therapy's efficacy.

The low adequacy of vitamin E and selenium intake among oncologic patients is a major concern, seeing that these nutrients play an important role in cellular protection and immunomodulation. Due to the treatment and to a rise in oxidative stress, cancer patients may have specific nutritional requirements. Beyond that, nutrient absorption may be compromised due to the side effects of treatments like chemotherapy and radiation. In a study by Bryan et al (2023)[22], that explored the efficacy of selenium and vitamin E supplementation in the prevention of recurrence and progression of bladder cancer, revealed no reduction of these parameters compared to placebo. The authors assumed that the absence of a positive effect may had been due to the complexity of the cancer's biology, emphasizing the need for more direct and personalized nutritional interventions for this population group. While Yuan et al (2022)[23], after providing vitamin E to experimental models, identified an improved efficacy of immunological therapies, suggesting that the inclusion of this resource may optimize the clinical outcomes of patients subjected to these types of treatments.

Conversely, the lack of a correlation between antioxidant intake and presence of adverse effects, as well as weight loss and BMI observed in the present study, reinforce the complexity of the nutritional impact of chemotherapeutic treatments, just as discussed by Bossi et al. (2021)[16], who identified malnutrition as a factor that can aggravate the adverse effects of cancer therapy. The present findings underpin the need for a continuous and individualized nutritional support, as suggested by Castillo-Martínez et al. (2018)[24], who support the use of nutritional assessment tools to identify and address the specific requirements of cancer patients.

CONCLUSION

In conclusion, the combination of a high prevalence of overweight, essential micronutrients deficiencies and the

complexity surrounding the treatment's side effects, reinforce the need for specific nutritional interventions and monitoring programs, with the objective of improving quality of life and clinical outcomes of oncologic patients.

STUDY LIMITATIONS

As study limitations, the small sample size and cross-sectional design restrict the generalizability of the findings and do not allow for the establishment of causal relationships. Nevertheless, the data obtained provide valuable support for future research in the field of oncology nutrition.

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