

Effect of Chocolate on Older Cancer Patients in Palliative Care: A Randomised Controlled Study

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Abstract

Background

Older advanced stage cancer patients, with changes in metabolic and nutritional status, represent an important demand for palliative care. The objective of the present study was to determine the effects of 4 weeks of chocolate consumption on the nutritional status, quality of life, body composition, oxidative stress and inflammatory activity of older cancer patients in palliative care.

Methods

Older cancer patients in palliative care with ambulatory monitoring were randomized to the following groups: control (CG, n = 15), intervention with 55% cocoa chocolate (IG1, n = 16) and intervention with white chocolate (IG2, n = 15) groups and evaluated before and after 4 weeks of treatment for nutritional status, food consumption, anthropometry, body composition, and laboratory parameters, and quality of life using the instrument of the European Organization for the Research and Treatment of Cancer.

Results

IG1 progressed with increased screening ($p < 0.01$) and nutritional ($p = 0.04$) scores on the Mini Nutritional Assessment tool. Anthropometry and body composition did not change. Regarding antioxidant capacity, reduced glutathione levels increased in IG2 ($p = 0.04$) and were higher than in IG1 ($p < 0.01$). Malondealdehyde levels were reduced in IG2 ($p = 0.02$) at the end of the study. Regarding quality of life, functionality improved in IG1, with a higher score in the functional domain ($p = 0.03$), and in the role functioning ($p < 0.01$) and in the social ($p < 0.01$) subdomains.

Conclusions

The consumption of chocolate with a greater cocoa content may contribute to the improvement of nutritional status and functionality among older cancer patients in palliative care. The consumption of white chocolate was associated with improved oxidative stress.

Trial registration:

ClinicalTrials.gov NCT04367493 - April 29, 2020. Retrospectively registered.

Background

Current projections indicate that, by 2060, about 16 million people per year will die of malignant neoplasias, representing a 109% increase compared to 2016 [1].

This will involve an increase in the number of patients, especially older adults, who will need palliative care for an appropriate management of the physical, psychosocial and spiritual effects of cancer in order to reduce the suffering and to improve the quality of life (QL) [2].

On this scenario, there is growing concern about the impact of nutrition on cancer patients receiving palliative care. Nutrition should preserve the nutritional status, prevent malnutrition and provide physical, emotional and psychological comfort by rescuing pleasure and convivial memories [3]. Nutritional assistance during palliative care focuses on the most comfortable manner of proceeding, respecting food preferences, beliefs and memories[4].

Some foods have been associated with benefits for general well-being, pleasure and emotional comfort [5]. The characteristic flavor, carbohydrate and fat content and highly palatable orosensory qualities of chocolate contribute to its definition as comfort food. Chocolate with a greater cocoa content has beneficial effects, acting against oxidative stress and systemic inflammation, which are risk factors for the progression of cancer [6]. In addition, chocolate can be considered to be an oral supplement by being a source of energy and nutrients, contributing to nutritional requirements [7].

Few studies are available about the impact of nutritional intervention on the QL of patients in palliative care, especially regarding supplements enriched with specific nutrients [8–10], with no studies on accessible consumed foods such as chocolate.

In view of this scenario, the objective of the present study was to assess the effects of chocolate consumption on the nutritional status of the older patients with cancer in palliative care, including food consumption, anthropometry and body composition, oxidative stress, inflammatory activity, and QL of older cancer patients in palliative care.

Methodology

This was a randomised, non-blind clinical trial conducted at the Services of Oncology and Palliative Care of the University Hospital of Ribeirão Preto, University of São Paulo. The study was approved by the Research Ethics Committee (9614/2015) and registered on www.clinicaltrials.gov (NCT04367493).

Inclusion criteria were: 60 years of age or older patients with cancer receiving ambulatory palliative care, with performance status (KPS) \geq 60%, > 70% prognosis of 30-day survival according to the Pap Score [11], with no chemotherapy and/or radiotherapy during the last 15 days, with normal thyroid function, able to eat orally, and no diagnosis of dementia.

Exclusion criteria were: tobacco and/or alcoholic drink use (\geq 3 weekly doses) during the last 3 months, cancer of gastrointestinal location involving the risk of obstructive factors affecting nutrition, and refusal to consume chocolate.

Sample size was based on studies of nutritional intervention with chocolate consumption which, however, had not investigated palliative care patients [12–15].

Subjects were pre-selected (n = 156) and 65 were invited to participate by the principal researcher. However, 19 were unable to start the protocol. Block randomization of 46 volunteers (2 blocks of 15 volunteers and 1 block of 16) was performed by the research coordinator using the "Research Randomizer" version 4.0 for the control group (CG), for the intervention group receiving 55% cocoa chocolate (IG1), and for the group receiving white chocolate (IG2). Allocation rate was 1:1:1. One individual in IG1 died during the study (Fig. 1).

IG1 patients were instructed to consume 25g of chocolate containing 55% cocoa daily for 4 weeks, while IG2 consumed 25g of white chocolate. CG was instructed not to consume chocolate. During the study the investigators did not interfere with the habitual food consumption of the patients. None of the volunteers habitually consumed chocolate before the study. Chocolate was supplied in 5 portions of 5g per day, for a total of 140 tablets.

The chocolate containing 55% cocoa provided a daily amount of 1337 mg polyphenols/ml GAE/patient [16]. IG1 received per day: 126 kcal; 12 g carbohydrates, 1.5 g proteins and 8.8 g total fats, while IG2: received 136 kcal; 14 g carbohydrates, 1.4 g proteins, and 8.3 g total fats. The patients recorded daily on a card the amount of chocolate consumed.

Primary outcome (nutritional status, including food consumption, anthropometry, and body composition) and secondary outcome measures (oxidative stress, inflammatory activity, and QL) were analyzed initially and after 4 weeks:

- **General and health characteristics:** sociodemographic and health status data.

- **Nutritional status:** Mini Nutritional Assessment (MNA), a method used for the geriatric population [17] and validated for the Brazilian population [18].

- **Food consumption:** 24-hour Diet Recall (24HR) and Food Frequency Questionnaire (FFQ). The FFQ was elaborated based on a food list, calibrated [19] and validated for older adults [20], applied only at the end of the study and used to assess the habitual diet consumed during the last 6 months. Nutrient consumption was estimated as: frequency of consumption x portion size x nutritional composition [20]. Food consumed was converted to grams and calculated with the Virtual Nutri Plus software updated with the data of the Brazilian Table of Food Composition [21]. The results obtained were compared to recommended intake of macro- and micronutrients for the age range [22].

The intake of total polyphenols was quantitated using the Phenol-Explorer databank, version 3.0 [23].

- **Anthropometric evaluation:** weight, height, body mass index (BMI) according to the cut-off points for older adults [24], arm circumference (AC), and calf circumference (CC).

- **Body composition:** determined by the deuterium oxide method after an 8-hour overnight fast. In the morning, each volunteer received 1 ml/kg deuterium oxide (99.9% deuterium oxide, Cambridge Isotope, USA) diluted to 7%, followed by 50 ml natural water for full ingestion of deuterium and mouth washing. Saliva samples were collected before and three hours after intake of the dose. The deuterium enrichment of the samples was determined by isotope ratio mass spectrometry (IRMS, Europa Scientific Hydra System, Cheshhire, UK) after equilibration with 100% hydrogen by the platinum-alumina catalyzer.

- **Routine clinical laboratory tests:** blood count, albumin, total proteins, sodium, potassium, and calcium ion.

- **Inflammatory activity:** serum levels of interleukin 6 (IL-6) were determined by ELISA with high sensitivity R&D Systems kits (Minneapolis, MN, USA). C-reactive protein was determined by the latex immunoturbidimetric assay.

- **Antioxidant capacity:** determination of reduced glutathione (GSH) [25] and ascorbic acid [26] levels.

- **Lipid peroxidation:** determination of malondialdehyde (MDA) levels [27].

- **Presence of DNA damage:** immunoassay with the DNA/RNA Oxidative Damage EIA Kit (Cayman Chemical) for the detection of all three oxidized guanine species based on 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels.

- **Quality of life:** application of the instrument of the European Organization for the Research and Treatment of Cancer (EORTC) - QLQ-C30 Questionnaire[28], with 30 questions including scales of overall health status, symptoms and function, with scores of 0 to 100. The higher these scores, the better the QL. High scores on the symptoms scale indicate a poorer QL (Authorization of the EORTC Quality of Life Group).

Data were analyzed statistically using the SAS Statistical Software, version 9.3 (SAS Institute, Inc. Cary, NC, USA) and the R Core Team (2016). Data were submitted to descriptive analysis, categorical variables were analyzed by the chi-square test, and a mixed effects linear regression model was used for group comparison at each time point and for comparison between time points in each group, adjusted for sex and age, with the level of significance set at < 0.05 .

Results

- Sociodemographic and clinical characterization of the sample

Mean patient age was 67.6 ± 5.7 years (range: 60–83 years) and mean KPS was $88.0 \pm 10.9\%$. Median time since cancer diagnosis was 43.5 months, while median time since the diagnosis of locally advanced or metastatic cancer was 11 months.

Mean chocolate consumption was 136 ± 8.3 tablets of 5 grams each for IG1 and of 135.8 ± 8.8 tablets for IG2. The sociodemographic and clinical characteristics of the patients are listed in Table 1, with no significant difference ($p > 0.05$) between groups.

Table 1
Sociodemographic and baseline clinical characteristics of older patients with cancer in palliative care

Variável	CG		IG1		IG2		Full sample	
	n	%	n	%	n	%	n	%
Gender								
Male	6	40.0	11	68.8	10	66.7	27	58.7
Female	9	60.0	5	31.3	5	33.3	19	41.3
Ethnicity								
Caucasian	13	86.7	15	93.8	11	73.3	39	84.8
Mulatto	2	13.3	1	6.3	1	6.7	4	8.7
Black	0	0	0	0	3	20.0	3	6.5
Education								
Illiterate	3	20.0	0	0	3	20.0	6	13.0
Up to 8 years	6	40.0	13	81.3	9	60.0	28	60.9
9 to 11 years	1	6.7	2	12.5	0	0	3	6.5
More than 11 years	5	33.3	1	6.3	3	20.0	9	19.6
Marital status								
Single	4	26.7	0	0	1	6.7	5	10.9
Married	6	40.0	11	68.8	8	53.3	25	54.3
Divorced	2	13.3	2	12.5	2	13.3	6	13.0
Widower	3	20.0	3	18.8	4	26.7	10	21.7
Religion								
Catholic	11	73.3	12	75.0	7	46.7	30	65.2
Evangelical	2	13.3	3	18.8	7	46.7	12	26.1
Spiritist	1	6.7	1	6.3	1	6.7	3	6.5
Other	1	6.7	0	0	0	0	1	2.2
Occupation								
Retired	11	73.3	8	50.0	13	86.7	32	69.6
Employee	4	26.7	8	50.0	2	13.3	14	30.4
Smoking habit								
Former smoker	9	60.0	9	56.3	11	73.3	29	63.0
Never smoker	6	40.0	7	43.8	4	26.7	17	37.0
Alcohol abuse								
Drank in the past	2	13.3	3	18.8	3	20.0	8	17.4
Never drank	13	86.7	13	81.3	12	80.0	38	82.6
Comorbidities								
Arterial hypertension	5	33.3	7	43.8	8	53.3	20	43.5
Dyslipidemia	2	13.3	2	12.5	2	13.3	6	12.9
Depressive disorder	1	6.7	1	6.3	3	20.0	5	10.9
COPD	0	0	2	12.5	3	20.0	5	10.9

CG: control group; IG1: intervention group 1 (chocolate with 55% cocoa); IG2: intervention group 2 (white chocolate); n: number; %: percentage; COPD = chronic obstructive pulmonary disease.

Variável	CG		IG1		IG2		Full sample	
	n	%	n	%	n	%	n	%
Hypothyroidism	3	6.5	1	2.2	0	0	4	8.7
Renal insufficiency	1	2.2	2	4.3	0	0	3	6.5
Heart disease	1	2.2	1	2.2	0	0	2	4.3
Dementia	0	0	0	0	1	2.2	1	2.2
Stroke sequel	0	0	0	0	1	2.2	1	2.2
Liver disease	0	0	1	2.2	0	0	1	2.2
Other	5	10.9	3	6.5	2	4.3	10	21.7
Primary tumor site								
Prostate	5	33.3	6	37.5	8	53.3	19	41.3
Breast	8	53.3	2	12.5	3	20.0	13	28.3
Lung	2	13.3	5	31.3	3	20.0	10	21.7
Kidney	0	0	3	18.8	1	6.7	4	8.7
Metastases								
Yes	12	80.0	16	100	11	73.3	39	84.8
Previous oncologic treatment								
Chemotherapy	11	73.3	13	81.3	8	53.3	32	69.6
Radiotherapy	11	73.3	4	25.0	9	60.0	24	52.2
Surgery	10	66.7	10	62.5	8	53.3	28	60.9
Hormone therapy	10	66.7	6	37.5	11	73.3	27	58.7
CG: control group; IG1: intervention group 1 (chocolate with 55% cocoa); IG2: intervention group 2 (white chocolate); n: number; %: percentage; COPD = chronic obstructive pulmonary disease.								

Almost all subjects (93.5%) were taking some type of medications, the more prevalent being antihypertensives (41.3%), nutritional supplements (41.3%), biphosphonates (39.1%), analgesics (37%), antidepressants (23.9%), laxatives (15.2%), and opioids (13%).

- Characterization of food intake and nutritional status

Estimated data of current and habitual macro- and micronutrient intake are presented in Table 2.

Table 2
Description of the nutritional information of current and habitual food consumption of older patients with cancer in palliative care

Variables	24HR STUDY BASELINE			24HR END OF STUDY			FFQ		
	Mean ± standard deviation			Mean ± standard deviation			Mean ± standard deviation		
	CG	IG1	IG2	CG	IG1	IG2	CG	IG1	IG2
Nº of meals/day	4.2 ± 0.7	4.4 ± 0.7	4.3	4.0 ± 0.9	4.5 ± 0.7	4.3 ± 0.9	4.3 ± 0.5	4.1 ± 0.4	4.1 ± 0.8
Kcal/Kg	22.2 ± 6.7	28.4 ± 8.9	25.7 ± 8.9	20.0 ± 6.3	29.6 ± 8.3	25.7 ± 8.3	24.2 ± 6.5	26.3 ± 2.8	25.1 ± 10.1
Protein/Kg	1.0 ± 0.5	1.2 ± 0.5	1.0 ± 0.5	0.9 ± 0.4	1.3 ± 0.6	1.1 ± 0.5	1.1 ± 0.3	0.9 ± 0.2	1.1 ± 0.5
Polyphenols(mg)	512.8 ± 163.4	508.7 ± 306.3	513.3 ± 301.2	489.0 ± 225.5	1880.5 ± 414.5	495.6 ± 244.1	577.4 ± 227.1	608.3 ± 168.3	502.6 ± 220.7
Fiber (g)	16.6 ± 8.8	19.4 ± 9.7	14.2 ± 8.8	16.6 ± 7.8	18.9 ± 9.8	15.1 ± 7.8	26.4 ± 10.4	20.7 ± 12.6	20.6 ± 13.7
% Adequation									
Fiber	66.6 ± 32.0	73.5 ± 40.5	50.9 ± 27.5	66.7 ± 27.2	74.3 ± 47.9	55.0 ± 25.0	98.4 ± 32.6	75.8 ± 46.9	71.2 ± 43.0
Vitamin A	46.6 ± 45.3	73.1 ± 85.3	38.9 ± 52.9	39.2 ± 32.7	61.2 ± 63.1	36.1 ± 37.2	63.9 ± 67.7	28.6 ± 34.1	31.9 ± 40.7
Vitamin B6	47.0 ± 39.2	82.5 ± 96.0	57.0 ± 41.7	43.2 ± 21.8	70.0 ± 44.5	41.9 ± 33.4	26.6 ± 13.6	35.4 ± 19.3	38.3 ± 23.9
Vitamin B12	56.9 ± 62.8	43.5 ± 72.7	17.8 ± 24.7	17.2 ± 16.6	121.6 ± 158.5	149.3 ± 312.9	35.1 ± 29.2	51.8 ± 46.5	54.6 ± 53.4
Vitamin C	202.4 ± 411.9	134.1 ± 153.3	74.5 ± 94.4	99.0 ± 96.0	139.1 ± 137.9	108.9 ± 108.6	170.9 ± 136.5	165.2 ± 141.9	126.8 ± 121.5
Vitamin E	56.6 ± 41.5	98.3 ± 87.8	47.6 ± 38.5	54.9 ± 41.7	73.8 ± 62.4	73.1 ± 48.8	26.5 ± 31.9	44.9 ± 62.6	29.4 ± 29.3
Calcium	33.6 ± 28.1	40.7 ± 15.6	46.2 ± 35.6	35.4 ± 21.5	53.9 ± 29.2	36.7 ± 24.4	44.1 ± 11.9	41.6 ± 16.6	35.3 ± 18.7
Sodium	178.4 ± 69.7	208.0 ± 85.4	188.5 ± 43.3	177.9 ± 55.8	209.2 ± 72.8	194.2 ± 73.5	191.1 ± 49.6	191.2 ± 19.0	193.8 ± 36.0

CG: control group; IG1: intervention group 1 (chocolate with 55% cocoa); IG2: intervention group 2 (white chocolate); 24HR: 24-hour Diet Recall; FFQ: Food Frequency Questionnaire; %: percentage; nº: number; Kcal: Kilocalorie; Kg: Kilogram; mg = miligram; g = gram.

At the beginning of the study, the energy and protein intake of more than half the volunteers (n = 25; 57.4% and n = 25; 57.4%, respectively) was below the daily recommendations. Mean daily calorie intake was 19.48 ± 4.20 kcal/kg current weight/day and mean protein intake was 0.66 ± 0.22 g /kg current weight /day.

Calorie consumption (Kcal/kg weight) was lower in CG after the intervention period (p = 0.01; 95% confidence interval (CI): +0.5 to + 3.9). Group comparison also showed that calorie consumption was lower in CG than in IG1 both at the beginning (p = 0.04; CI= -11.9 to -0.4) and at the end (p < 0.01; CI= -15.1 to -3.5) of the study.

At the end of the study, polyphenol consumption increased in IG1 (p < 0.01; CI= -1480.2 to -1233) and was higher than in CG (p < 0.001; CI= -1586.2 to -1165.4) and IG2 (p < 0.01; CI = + 1158.8 to + 1579.6).

Except for sodium, the intake of fibers, calcium and of all vitamins analyzed (A, B6, B12, C and E) was below recommended levels.

Regarding nutritional status, initially 43.5% of the patients were at risk (n = 15; 32.6%) or were malnourished (n = 5; 10.9%) according to the MAN tool. However, at the beginning of the study, IG1 patients had a lower score at screening (p < 0.01; CI = + 0.5 to + 2.8) and during nutritional assessment (p = 0.04; CI = + 0.1 to + 4.1) with the MAN tool compared to CG. IG1 patients showed an increase in the screening (p < 0.01; CI= -2.2 to -0.4) and nutritional assessment (p = 0.04; CI = + 0.1 to -4.1) scores at the end of the study (Table 3).

Table 3
Anthropometric evaluation, body composition and nutritional status of older patients with cancer in palliative care

VARIABLES	STUDY BASELINE			END OF STUDY		
	Mean ± standard deviation			Mean ± standard deviation		
	CG	IG1	IG2	CG	IG1	IG2
Anthropometric evaluation						
Body mass index (Kg/m ²)	29.3 ± 4.5*	26.2 ± 4.0	26.1 ± 3.7	29.3 ± 4.4**	26.3 ± 3.5	26.3 ± 3.8
Arm circumference (cm)	32.4 ± 3.2	30.6 ± 3.5	29.8 ± 3.5	32.2 ± 3.4	30.7 ± 2.8	30.1 ± 3.2
Calf circumference (cm)	37.5 ± 3.0	36.9 ± 3.9	37.5 ± 2.8	37.5 ± 3.1	37.2 ± 3.4	37.3 ± 3.2
Body composition by deuterium						
Total body water (%)	49.3 ± 7.0	48.9 ± 8.1	47.8 ± 7.0	51.5 ± 9.4	48.5 ± 7.4	48.9 ± 5.4
Fat mass (%)	32.7 ± 9.6	33.2 ± 11.1	34.7 ± 9.6	29.6 ± 12.8	33.7 ± 10.1	33.2 ± 7.3
Lean mass (%)	67.3 ± 9.4	66.8 ± 11.1	65.3 ± 9.6	70.4 ± 12.8	66.3 ± 10.1	66.8 ± 7.3
MNA Screening						
Score (mean ± standard deviation)	11.2 ± 1.4 ^δ	9.5 ± 2.4 ^β	10.5 ± 1.8	11.6 ± 0.6	10.9 ± 1.2	11 ± 1.5
Nutritional status						
Normal	10 (66.7)	9 (56.2)	7 (46.7)	10 (66.7)	8 (53.3)	9 (60.0)
At risk of malnutrition	5 (33.3)	3 (18.7)	7 (46.7)	5 (33.3)	7 (46.7)	6 (40.0)
Malnourished	0 (0)	4 (25.0)	1 (6.7)	0 (0)	0 (0)	0 (0)
MNA Total Assessment						
Score (mean ± standard deviation)	24.7 ± 1.8 ^α	22.6 ± 3.9 [∞]	23.9 ± 3.1	25.4 ± 1.5	24.7 ± 2.3	25.1 ± 2.5
Nutritional status						
Normal	11 (73.3)	9 (60.0%)	9 (60.0%)	12 (80.0)	10 (66.7)	13 (86.7)
At risk of malnutrition	4 (26.7)	5 (33.3)	5 (33.3)	3 (20.0)	5 (33.3)	2 (13.3)
Malnourished	0 (0)	2 (13.3)	1 (6.7)	0 (0)	0 (0)	0 (0)
CG: control group; IG1: intervention group 1 (chocolate with 55% cocoa); IG2: intervention group 2 (white chocolate); n: number; %: percentage; Kg: Kilogram; MNA: Mini Nutritional Assessment .						
* p = 0.04 vs. IG1 and IG2; ** p = 0.03 vs. IG1; ^δ p < 0.01 vs. IG1; ^α p = 0.04 vs. IG1; ^β p < 0.01 baseline vs. end; [∞] p = 0.04 baseline vs. end.						

At the beginning, CG had a higher BMI than IG1 (p = 0.04; CI = +0.1 to +6.0) and IG2 (p = 0.04; CI = +0.2 to +6.1), which continued to be higher than that of IG1 (p = 0.03; CI = +0.4 to +6.3) at the end of the study (Table 3).

- Laboratory exams and QL

Table 4 presents the results of the laboratory tests. After the 4 weeks of the study, there was an increase in 8-OHdG in all groups: CG (p < 0.01; CI = -2.2 to -0.4), IG1 (p < 0.01; CI = -2.0 to -0.3) and IG2 (p = 0.04; CI = -1.8 to -0.02).

Table 4
Description of the results of laboratory tests of older patients with cancer in palliative care

VARIABLES	STUDY BASELINE			END OF STUDY		
	Mean ± standard deviation			Mean ± standard deviation		
	CG	IG1	CG	IG1	CG	IG1
Hemoglobin (U/dL)	13.0 ± 1.3	12.7 ± 1.8	12.5 ± 2.1	13.0 ± 1.4*	12.3 ± 1.8	12.6 ± 1.5
White blood cells (x103/μL)	5.9 ± 2.0	7.3 ± 3.4	5.7 ± 1.8	6.0 ± 2.0	6.08 ± 2.0	7.0 ± 3.2
Lymphocytes (x103/μL)	1.5 ± 0.4	1.9 ± 0.6	1.8 ± 0.7	1.6 ± 0.5	1.68 ± 0.5	1.7 ± 0.5
Total proteins (U/dL)	6.8 ± 0.5	6.7 ± 0.7	6.9 ± 0.6	6.9 ± 0.4	6.69 ± 0.7	7.0 ± 0.7
Albumin (U/dL)	4.2 ± 0.3*	4.0 ± 0.4	4.1 ± 0.3	4.2 ± 0.2*	4.0 ± 0.3	4.2 ± 0.3
Vitamin (mg/dL)	0.3 ± 0.1**	0.2 ± 0.1	0.2 ± 0.1	0.4 ± 0.1**	0.2 ± 0.1	0.2 ± 0.1
C-reactive protein (mU/dL)	0.4 ± 0.5	2.4 ± 4.0	1.8 ± 3.4	0.9 ± 1.2	2.4 ± 3.0	1.4 ± 3.2
8-OHdG (ng/mL)	4.6 ± 2.2 ^δ	4.9 ± 2.2 ^δ	4.4 ± 1.6 ^β	5.9 ± 2.6	6.0 ± 2.0	5.3 ± 1.4
MDA (μM)	10.9 ± 3.3	14.4 ± 10.2	15.6 ± 11.9 ^α	9.1 ± 2.6	11.3 ± 3.0	10.8 ± 4.8
GSH (μM)	9.8 ± 1.4	9.0 ± 1.8	10.0 ± 11.1 ^{β α}	10.3 ± 2.0	8.8 ± 1.5 [∞]	10.7 ± 2.1
Interleukin 6 (pg/mL)	51.8 ± 38.6	136.6 ± 182.3	65.21 ± 132.49	87.2 ± 125.6	154.8 ± 208.4	38.7 ± 25.0
CG: control group; IG1: intervention group 1 (chocolate with 55% cocoa); IG2: intervention group 2 (white chocolate); 8-OHdG: 8-hydroxy-2'-deoxyguanosine; MDA: malondialdehyde; GSH: reduced glutathione; μL: microliter; U: unit; dL: deciliter; mU: miliunit; mg: miligram; μM: micromol; pg: picogram; mL: milliliter.						
* p = 0.03 vs. IG1; ** p < 0.01 vs. IG1 e IG2; ^δ p < 0.01 baseline vs. end; ^α p = 0.02 baseline vs. end; ^β p = 0.04 baseline vs. end; [∞] p = 0.02 vs. CG e < 0.01 vs. IG2.						

Regarding the antioxidant capacity, GSH levels were lower in IG1 than in CG (p = 0.02; CI = + 0.2 to + 2.9) and IG2 (p < 0.01; CI = -3.4 to -0.7) at the end of the study, with an increase in IG2 (p = 0.04; CI = -1.6 to -0.02). In contrast, vitamin C levels were lower in the intervention groups than in CG at the beginning (p < 0.01; CI = 0.07 to 0.2 between IG1 and CG; CI = 0.08 to 0.2 between IG2 and CG) and at the end of the study (p < 0.01; CI = 0.1 to 0.3 between IG1 and CG; CI = 0.1 to 0.3 between IG2 and CG).

Lipid peroxidation, determined according to MDA levels, was reduced in IG2 (p = 0.02; CI = + 0.7 to + 9.1) from the beginning to the end of the study and IL-6 levels were higher in IG1 (p = 0.03; CI = + 12.9 to + 219.3) than in IG2 at the end of the study.

The QL of IG1 patients (Table 5) improved in terms of functionality, with a higher score for the functional domain (p = 0.03; CI = -13.3 to -0.7), the role functioning subdomain (p < 0.01; CI = -36.4 to -6.3), and the social subdomain (p < 0.001; CI = -28.8 to -4.8).

Table 5
Score of quality of life domains of older patients with cancer in palliative care

DOMAINS	STUDY BASELINE			END OF STUDY		
	Mean ± standard deviation			Mean ± standard deviation		
	CG	IG1	IG1	CG	IG1	IG2
Global health status	83.9 ± 16.2	79.7 ± 12.9	75.6 ± 17.1	79.4 ± 23.1	83.3 ± 11.4	82.2 ± 16.3
Functional	83.6 ± 12.4	75.6 ± 17.3 ^β	82.1 ± 14.2	82.1 ± 13.5	82.7 ± 8.9	83.1 ± 17.0
Physical functioning	84.0 ± 15.3	72.5 ± 19.2	84.9 ± 16.4	84.9 ± 18.4	80.0 ± 18.0	82.7 ± 22.4
Role functioning	94.4 ± 12.1 [*]	60.4 ± 37.5 ^{**∞}	82.2 ± 24.8	82.2 ± 29.9	83.3 ± 20.9	88.9 ± 24.1
Emotional functioning	77.8 ± 28.1	82.8 ± 25.4	74.4 ± 23.2	73.9 ± 30.5	78.9 ± 16.9	75.0 ± 27.6
Cognitive functioning	78.9 ± 23.1	86.5 ± 17.5	82.2 ± 24.0	87.8 ± 14.7	90.0 ± 12.3	87.8 ± 18.3
Social functioning	87.8 ± 24.8	72.9 ± 28.5 ^{δ∞}	90.0 ± 18.7	85.6 ± 27.4	88.9 ± 13.6	90.0 ± 16.4
Symptom	9.6 ± 9.5 ^α	18.3 ± 11.6	14.0 ± 14.4	12.0 ± 12.0	14.9 ± 10.2	12.0 ± 13.5

CG: control group; IG1: intervention group 1 (chocolate with 55% cocoa); IG2: intervention group 2 (white chocolate).

* p < 0.01 vs. IG1; ** p = 0.03 vs. IG2; ^δ p = 0.04 vs. IG2; ^α p = 0.05 vs. IG1; ^β p = 0.03 baseline vs. end; [∞] p < 0.01 baseline vs. end.

There was no deleterious effect that could be attributed to the consumption of dark or white chocolate, such as nausea, vomiting, diarrhea, or epigastric pain.

Discussion

The present study, conducted on older cancer patients in palliative care with preserved functionality, demonstrated benefits in terms of improved nutritional status and QL in the group ingesting chocolate with a higher percentage of cocoa. IG1 showed an increased estimated polyphenol intake at the end of the intervention compared to CG and IG2. Several studies that used the values of the Phenol-Explorer databank or values measured by HPLC have reported a daily polyphenol intake ranging from 377 ± 15 to [29] 1756.5 ± 695.8 [30] mg/day in many countries [29–31]. However, all studies were conducted on healthy subjects, with no study on palliative care cancer patients. Considering that the mean worldwide intake of polyphenols is approximately 1 g/day, the present study detected a habitual daily intake of two to three times less, in agreement with the result reported in a Brazilian population study [29].

In addition, except for sodium, the intake of fibers, calcium and of all vitamins analyzed (A, B6, B12, C and E) was below recommended levels. With aging and progression of oncologic disease, modifications may occur in food consumption due to factors such as loss of appetite, sensory changes in gustatory and olfactory capacity, and social, emotional and economic aspects such as social isolation and depression, with a consequent reduction of the intake and absorption of micronutrients essential for health [32, 33].

However, the opposite was observed regarding sodium intake, which was excessive in all groups. This result has been associated with the increased consumption of processed and ultraprocessed foods by the population [34], with 80% of Brazilian older males and 61% of Brazilian older females habitually consuming higher than recommended sodium amounts [34].

Energy and protein consumption was lower than recommended in more than half the patients at the beginning and at the end of the study.

At the beginning and at the end of the study, CG showed lower calorie consumption per Kg than IG1 even with a higher BMI, a higher MAN score and albumin value and better functionality. Despite the difficulty in interpreting this finding, we believe that IG1 had a greater consumption per Kg as a form of compensation for its worse basal nutritional status. On the other hand, it has been demonstrated that reduced food intake or low energy intake is independently associated with weight loss in oncologic patients during progression of the disease [35, 36].

According to the MAN nutritional screening, most participants had an adequate nutritional status both at the beginning and at the end of the study. Previous studies have reported higher proportions of malnutrition among cancer patients in palliative care. However, those studies were more heterogeneous regarding the primary location of the tumor, nutritional assessment methods, and functionality [37–39]. This divergence may be attributed to the inclusion criteria of the present study.

At the beginning of the study, IG1 subjects had lower screening and nutritional assessment scores determined by the MAN tool and lower BMI and albumin values compared to the other groups. However, at the end of the intervention period, their screening score and MAN results were increased. Nutritional intervention can reduce the weight loss of patients in an advanced stage of cancer and improve their nutritional status [40].

No differences in body composition were observed here between groups, possibly owing to the short period of intervention. Nevertheless, it should be pointed out that changes in body composition in response to changes in the metabolic demand, physiological changes, aging and alterations due to cancer treatment are frequent among older adults receiving palliative care and should be monitored [41].

Laboratory work-up demonstrated progression of oncologic disease. 8-OHdG levels were significantly increased in all groups, being possibly associated with the evolution of cancer patients [42].

After the period of intervention, IG1 showed an increase in the levels of the proinflammatory cytokine IL-6 with a concomitant reduction of the antioxidant defense compared to the other groups. These results suggest a worse clinical situation of these patients who already showed greater nutritional impairment at the beginning of the study. Systemic inflammation is associated with worse clinical outcomes, including reduced survival, of cancer patients [43]. GSH and vitamin C play a prominent role in cell protection against cytotoxic and carcinogenic substances [44].

Oxidative stress activates the inflammatory pathways that lead to the transformation of a normal cell into a neoplastic one, also affecting survival, proliferation, invasion, angiogenesis, and resistance to oncologic treatment [45]. Conversely, there is evidence that circulating IL-6 levels may also affect the antioxidant defense system [46]. During the final phase of the study, IL-6 levels were found to be significantly lower in IG2 compared to IG1. In agreement, the levels of MDA, a product of lipid peroxidation, were significantly reduced and GSH was increased in the white chocolate group.

We believe that the beneficial action of white chocolate consumption on systemic inflammation and the defense against oxidative stress may be the effect of some not yet studied component. The benefits of white chocolate intake were also observed in a study by OSTERTAG et al. (2013) [47] conducted on healthy subjects, showing that the consumption of 60 grams of white chocolate in a single intake contributed favorably to platelet activation and to bleeding time compared to bitter chocolate. Since white chocolate does not contain flavonoids, the authors suggested that other compounds such as milk serum protein may be responsible for antiplatelet effects [47]. Thus, we may consider white chocolate not to have a placebo effect, except for the evaluation of the polyphenol consumption.

Regarding the QL of the patients, IG1 progressed to higher scores in the functionality domain and subdomains, suggesting that the consumption of chocolate with a higher cocoa content was of benefit in terms of QL.

In a previous study, the authors observed low scores on global and functional health scales, with role functioning showing the worst evaluation, as well as high scores on the symptom scale [48]. In the present study, volunteers showed a good QL according to the global health scale and role functioning score, and the initial symptom score was low.

Few studies have analyzed the effect of dark chocolate consumption on QL, but some publications have suggested that supplementation with high cocoa chocolate can be of benefit [49, 50].

Strengths and limitations of the study:

This was a randomized, controlled study of nutritional intervention with chocolate. To date, we have not found any other studies that evaluated this intervention in older adults with cancer in palliative care. The limitations of the present study were a small number of subjects and a short period of intervention. However, this is an inherent difficulty of clinical studies in palliative care. We suggest that further interventions should explore the relations and the underlying causal mechanisms regarding chocolate consumption and its effects on the health and QL of older patients on palliative care.

The present results demonstrate that the consumption of chocolate with a higher cocoa content may contribute to improved nutritional status and functionality among older cancer patients in palliative care with > 70% prognosis of 30-day survival. The consumption of white chocolate was associated with an improvement of oxidative stress parameters.

Good adherence to the consumption of both chocolate types was observed during the study, this being a viable and pleasurable food of easy access contributing to the food supply and well-being of the patients.

Considering that food preferences are highly personal, we believe that nutritional support should also be adapted to the necessities, wishes and preferences of everyone in order to be effective and applicable to the reality of each one. In this respect, nutritional assistance can be an opportunity to aid the patients and their families during treatment.

Declarations

Ethics approval and consent to participate.

The study was approved by the Research Ethics Committee of HC-FMRP-USP (Protocol No. 9614/2015) and all subjects gave written informed consent to participate. This research was registered at www.clinicaltrials.gov (NCT04367493).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Authors' contributions

JV: was responsible for conception and design of the study, collected data, and wrote the main manuscript.

LS: collected data, performed laboratory tests and analyzed the data.

KP: collected data, performed laboratory tests and analyzed the data.

AJJ: collected data, performed laboratory tests and analyzed the data.

PLJ: collected data, performed laboratory tests and analyzed the data.

EF: was responsible for the conception and design of the study.

JM: wrote the main manuscript text and prepared figure and tables

NL: conception and design of the study and wrote the main manuscript

All authors have read and approved the submitted version of the manuscript and they agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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Figures

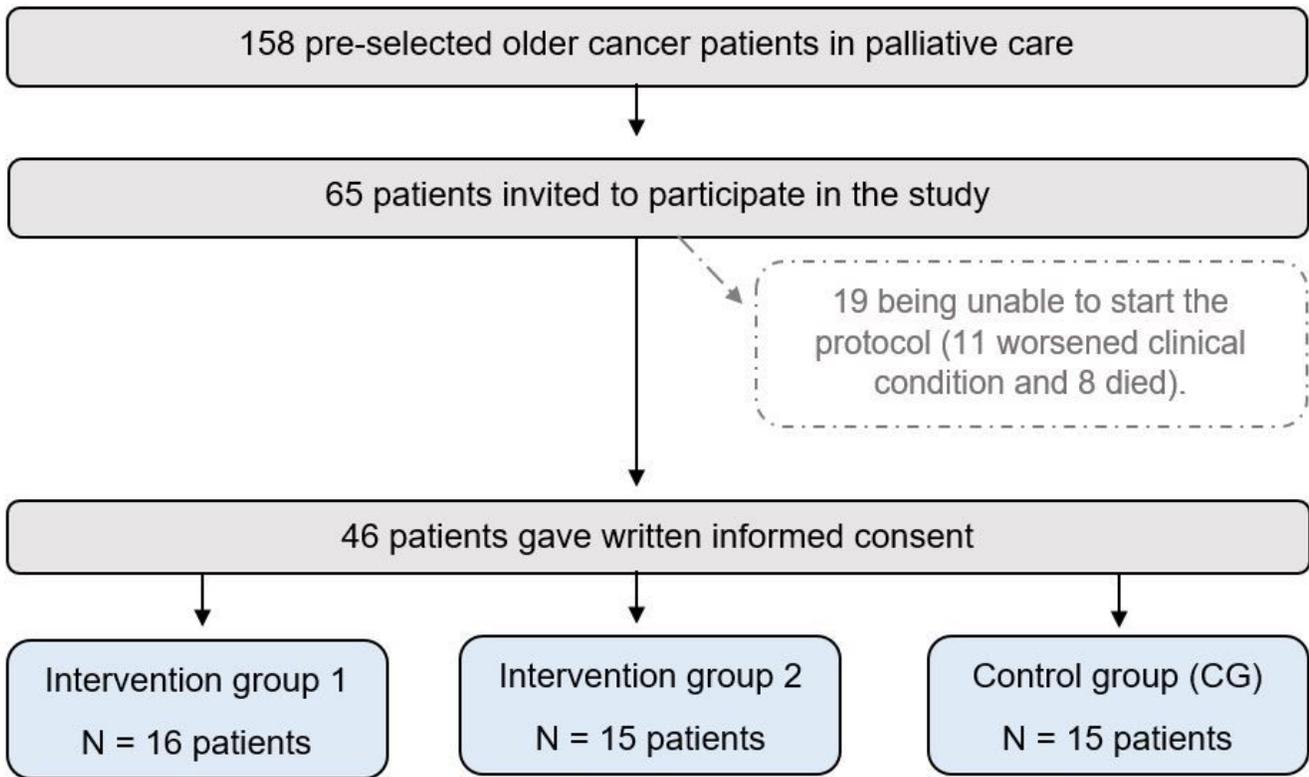


Figure 1

Flowchart of the insertion of patients in the groups during the study period