Immax

MONOGRAPH

- + Does not alter the taste
- + Improves palatability
- + Avoids the loss of lean body mass

Zinc
L-leucine
Proteins

10 years

NEW POSSIBILITIES FOR LIFE

prodiet
CLINICAL NUTRITION

Immax

PROMOTE WELLBEING WITH THE AID OF IMMAX

Fortifying nutrients which do not alter the taste of the food.
It can be added in sweet or salty preparations.

INDEX

INTRODUCTION

There are **596 thousand** new cases of **CANCER** between 2016 and 2017 in **Brazil**.

According to the World Health Organization, human malignant neoplasia has become one of the main causes of morbi-mortality, attaining approximately 14 million people per year in the world, lung, prostate, bowel and stomach cancer being the most common among men and breast, bowel, lung and neck of the uterus the most common types in women. In Brazil, an estimate of the National Cancer Institute - INCA, for 2016 and 2017, indicates the occurrence of around 596 thousand new cases of cancer (Figure 1).

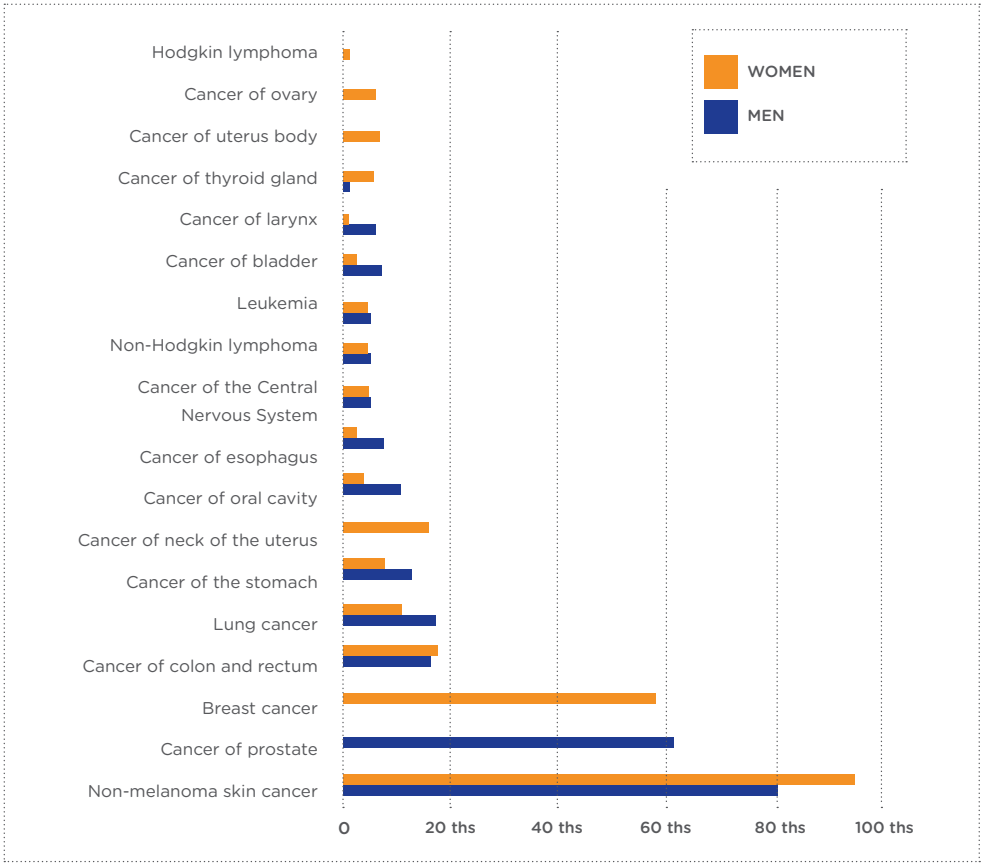


Figure 1: *Estimate of incidence of cancer for Brazil, 2016-2017.* ***Source****: INCA*[1]

According to this same source, the incidence of the disease has increased in recent years. **The number of deaths in Brazil due to cancer has increased 31% since 2000 and reached 223.4 thousand people per year at the end of 2015, occupying second place in cause of death in the country**[1]**.**

Due to these figures, cancer has been considered by many to be a public health problem, especially as it can be prevented, or even avoided, with educational measures of the population to control environmental carcinogenic agents and healthy life habits, as suitable nutrition and physical exercise, etc.[2,3]. The Union for International Cancer Control (UICC) stated in its latest report that more than a third of the most common types of cancer can be prevented through diet, maintenance of healthy weight and regular practice of physical activity[4].

The success of the therapy employed is directly related to the nutritional state of the oncological patient. The aggressiveness and localization of the tumor, the organs involved, the clinical, immunological and nutritional conditions imposed by the disease and made worse by late diagnosis and the therapy are factors which can jeopardize the nutritional state, with serious prognostic implications, and interfere directly in the treatment[2,3].

MORE THAN

1/3

of the types of cancer can be prevented through **diet,** maintenance of **healthy weight** and regular practice of **physical activity.**

NUTRITIONAL STATE OF ONCOLOGICAL PATIENT

In the Brazilian Oncological Nutrition Inquiry, of INCA, of 2013, 4,822 oncological patients admitted in 45 Brazilian institutions were evaluated, by means of the Patient Generated - Subjective Global Assessment (PG-SGA). Malnutrition or nutritional risk were present in 2,176 (45.1%) patients studied[5]. PG-SGA is one of the tools validated for nutritional evaluating and sorting for oncological patients.

In this context, the new guideline of ESPEN 2016 orients the use of NRS 2002 and of Nutrition Risk in the Critically Ill (Nutric score)[6].

In a recent analysis with more than 8160 European and Canadian oncological patients the researchers developed a classification system far loss of weight in cancer which incorporates dimensions of percentage of weight loss (%WL) and of Body Mass Index (BMI) and links them to survival (Figure 2). The data represents the spectrum of these features in patients with cancer and showed that **%WL and BMI foresee the survival regardless of the conventional prognostic factors, including the cancer's location, stage and performance status[7].**

The catabolic alterations in the patient with cancer begin by inadequate nutritional consumption which is characterized as being present, if the patient cannot eat for more than a week, or if the consumption is less than 60% of the energy requirement for more than one or two weeks[6].

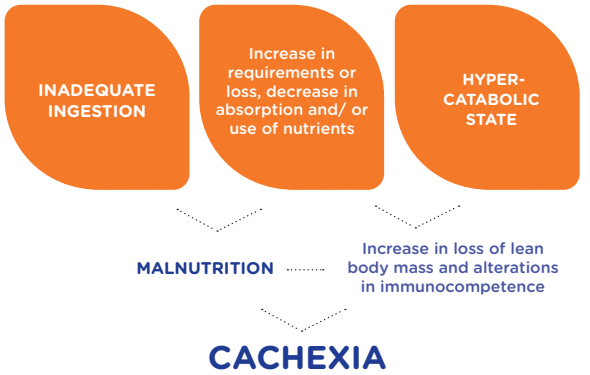
The oncological patient can also have an increase in requirements or loss, decrease in the absorption and/or use of nutrients and Immunoinflammatory response which increases metabolism, generating a hypercatabolic inflammatory state[8].

The presence of the syndrome anorexia-cachexia is often a complication in the advanced states of neoplatic disease .

% weight loss \ BMI (kg/m²)	≥28	25 to 27,9	22 to 24,9	20 to 21,9	<20
≤2,4	0	0	1	1	3
2,5 to 5,9	1	2	2	2	3
6 to 10,9	2	3	3	3	4
11 to 14,9	3	3	3	4	4
≥15	3	4	4	4	4

Figure 2: *The average survival times by grade were as follows: Grade 0: 20.9 months; Grade 1: 14.6 months; Grade 2: 10.8 months; Grade 3: 7.6 months and Grade 4: 4.3 months. P<.001. Adapted from 7.*

Figure 3: Development of cachexia in oncological patient (Source: 8 and 9).



Cachexia is defined as a multifactoral syndrome characterized by constant and progressive loss of skeletal lean body mass (accompanied or not by loss of fat mass), which cannot be totally reverted by means of conventional nutritional support, and has as a consequence the loss of functional capacity of the individual. The physiopathology involved in the syndrome is described as a negative proteic and energy balance, resulting from a combination of variables as reduced food ingestion and a series of metabolic alterations[10]. The latter are caused by complex interactions between inflammation (pro-inflammatory cytokines), neurohormonal alterations and factors potentially proteolytic and lipolytic produced by the tumor and its host[11]. Cachexia of cancer is a continuous process and has three stages of clinical relevance: precachexia, cachexia, and refractory cachexia. Not all patients undergo all these stages, which can be described in the following manner (TABLE 1)[12].

TABLE 1: *Classification of Neoplastic Cachexia*

TYPE	DESCRIPTION
Precachexia	Anorexia, intolerance to glucose
Cachexia	Unintentional recent weight loss exceeding 5% of customary in the last 6 months, or body mass index (BMI) less than 20 kg/m² associated with unintentional recent weight loss exceeding 2% or sarcopenia associated with recent weight loss exceeding 2%
Refractory Cachexia	Result of terminal disease or when, in the presence of rapidly progressive disease, it does not respond to antineoplastic therapy; index ECOG* 3 or 4 associated with life expectancy of less than 3 months

** ECOG - Eastern Cooperative Oncology Group*

NUTRITIONAL STATE OF ONCOLOGICAL PATIENT

Weight loss is reported as being the predominant factor regardless of poor prognosis[13,14] and up to 20% of all deaths related to cancer arise from cachexia[15,16,17]. At the moment of the diagnosis, approximately 80% of the patients with tumors in upper GIT have substantial weight loss. The frequency and severity of the malnutrition are greater in those with malignant as gastrointestinal and lung diseases, there being less risk of weight loss in those with breast cancer, leukemia, sarcoma and lymphoma[18]. **Neoplastic patients, besides the factors related to the disease, those related to the treatment also contribute to the worsening of the nutritional state by interference in food ingestion.**

Approximately 30% of chemotherapeutic agents induce nausea and vomiting, cisplatin being considered to be the agent of greatest emetogenic potential. Diarrhea and mucositis occur due to the action of the chemotherapeutic agents in the cellular cycle of cells of quick division, leading to functional mucous alterations. The chemotherapeutic agents most associated with diarrhea are: cytarabine, fluorouracil, topotecan, actinomycin D, oxaliplatin and nitrosoureas. Mucositis is associated with odynophagia, bleeding and local infection, having as main agents o methotrexate, fluo- rouracil, bleomycin, doxorrubycin, cisplatin, vincristine and vimblastine. Xerostomia is caused by the competition of the chemotherapeutic agents with receptors of acetylcholine neurotransmitters, which prevent the transmission of parasympathetic impulses of the salivary cells and occurs more frequency in women and the elderly[19].

Radiotherapy, when employed, is also associated with symptoms and alterations which impair appropriate nutrition. The alterations occurring can be countless, and are related to the place irradiated, as per TABLE 2 at the side:

TABLE 2: Adverse effects of Radiotherapy

PLACE	ADVERSE EFFECTS
CENTRAL NERVOUS SYSTEM	Anorexia, nausea, vomiting
HEAD AND NECK	Mucositis, dysphagia, xerostomia, odynophagia, dysgeusia, dysosmia, anorexia.
THORAX	Dysphagia, odynophagia, esophagitis, nausea, vomiting.
ABDOMEN AND PELVIS	Nausea, vomiting, diarrhea, fistulas, actinic enteritis.

Adapted from Augusto ALP, In: Cotrim, TH[20].

The loss of muscle mass (also known as sarcopenia), which can be accompanied by loss of function and strenght, is directly related to the increase of toxicity to chemotherapy, including in the obese. Sarcopenic obesity is present in 15 to 36% of the obese with neoplasia. The outcomes associated with such condition are, besides greater toxicity to chemotherapy, an increase in the occurrence of surgical complications, physical incapacity and reduced global survival [21,22]. Besides neoplasia, muscular catabolism is a serious complication of a variety of other diseases and conditions, such as cardiac insufficiency, sepsis, besides aging, situations of disuse and muscular dystrophy[23]. These other conditions, are often superimposed in oncological patients, worsening their nutritional state. **Regardless of the cause, the proteic degradation is associated with impairment of life quality and poor prognosis of associated pathologies.**

NUTRITIONAL INTERVENTION IN ONCOLOGICAL PATIENTS

Considering the impact of the nutritional state on the treatment and evolution of neoplastic diseases, early and suitable nutritional intervention becomes essential, as indicated by the guideline of ESPEN for the oncological patient of 2016[6]. In accordance with that stipulated, the nutritional intervention must include nutritional advice, the treatment of the symptoms of the gastrointestinal tract which impair food ingestion and the indication of nutritional supplement, aiming at increasing oral supply.

Feeding by oral means is the most physiological manner of increasing the daily nutritional provision. Nevertheless, it is not always possible to attain the requirement only by means of food in individuals affected by advanced age, fragility, chronic diseases, and the effects of anti-neoplastic therapy.

Baldwin et al [24] Ravasco et al [25] found that individualized nutritional advice associated with the use of oral nutritional supplements (SNO), separately or together, are two of the strategies aiming at increasing the daily proteic and energy supply. In the meta-analysis of Baldwin, the studies were able to indicate that the nutritional intervention was associated with a large energy increase of 430 kcal/day, a weight gain of 1.9kg, **besides the positive effect on the patient's life quality.**

IMMAX provides daily **630 kcal** and **39,4 grams** of **PROTEINS.**

BENEFITS OF WHEY PROTEIN

The isolate whey protein leads to large benefits for the patient in nutritional therapy, as the capacity of promoting better gastric emptying. The latter is quicker, nevertheless, the remaining in the bowel is increased, which ensures a better digestion and absorption, attaining higher levels of circulating amino acids, i.e., greater retention of nitrogen, quicker than other sources of protein [26, 27, 28].

The anticarcinogenic, immunostimulatory and anti-inflammatory effects of whey protein and its peptides have been extensively studied for prevention and treatment of cancer in models in vitro, animals and in humans [26, 27, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39].

A study with intestinal Caco-2 cells showed that whey protein had an anti-inflammatory effect by reducing the production of IL-8[26]. In their recent work, Silva et al[27] used models of human umbilical vein endothelial cells (HUVEC) with response TNF-α induced or not, showing that whey protein have several effects in inflammatory gene expression. The beneficial effect of whey protein can be mediated by the presence of branched-chain amino acids (BCAA), by reducing the inflammatory response in model HUVEC with response TNF-α induced.

A recent review of 52 clinical studies in humans supports the idea that dairy products have better anti-inflammatory effects in individuals with metabolic disturbances than in healthy individuals. In accordance with the categories of dairy products the data stratification showed that as opposed to the high fat content products, **none of the results from studies with low fat content products indicated a pro-inflammatory activity.** The pro-inflammatory activity identified in the group with whole fat dairy products was attributed mainly to the presence of saturated fat. In the review 50 inflammatory markers possibly involved in the effects investigated were identified[40]. The reduction of the inflammation of low degree in healthy adults was also correlated with the ingestion of dairy products in the stud ATTICA (3,042 individuals)[41].

Another recent review showed a series of benefits of whey protein besides anti-inflammatory, immunostimulatopry and antitumor properties, as antioxidant, hypotensive, intestinal homeostatic, anti-obesity, antidiabetic, muscular biosynthesis, osteoprotective and dermo-protective[42].

The supplementation with whey protein was studied in the capacity of pre-operatory functional progress and recovery in cancer patients undergoing colorectal resection for cancer showing significant clinical improvements in the patients[43].

IMMAX

has 60% Isolated Whey Protein, 23% Concentrate Whey Protein and 17% L-leucin in its proteic composition, with only 3% of saturated fat in the lipid composition.

THE ROLE OF LEUCINE IN CACHEXIA

The reduced active synthesis of proteins receives the term anabolic resistance and can be seen in conditions as immobilization, aging, cachexia of cancer and sepsis[4].

Cachectic patients in parenteral nutrition (PN) supplemented with branched-chain amino acids (BCAA) showed an increase in the flow of leucine and proteic synthesis, while protein breakdown remained stable[45]. Another study with patients in PN showed improvement in the proteic development and synthesis of albumin in patients supplemented with BCAA[46].

In oncological patients losing weight, the administration of amino acids (including doses of branched-chain amino acids) seems to have been beneficial related to loss of muscle mass and proteic synthesis, as per review published by Bozzetti[47].

Leucine is studied as the BCAA with the greatest role in proteic synthesis[48]. In a recent study, supplementation with leucine preserved the anabolic cellular signaling during periods of physical inactivity and had a partial protective effect in body composition and results of the muscle function[49].

In the elderly it is well debated that supplementation with leucine improves the response of muscle proteic synthesis[50, 51, 52, 53, 54]. In this context, Bauer[55] used supplementation of vitamin D, with 40 grams of whey protein + 6 grams of leucine.

In mice with tumor, supplementation of leucine provides significant protection of skeletal muscle mass[56]. Recent work in humans suggests that patients with cachexia induced by anabolic resistance and impaired muscular anabolism benefit from the simultaneous supplementation of insulin and amino acids[57].

Some mechanisms possibly involved in the regulatory effects of leucine on proteic synthesis are: the increased availability of substratum and secretion of anabolic hormones as insulin; and the modulation of anabolic routes in skeletal muscle[44].

The daily dose of **IMMAX provides 7,2 grams of LEUCINE**

NUTRITIONAL SUPPLEMENTATION IN ONCOLOGY AND ZINC.

Present in enzymes and proteins which participate in the metabolism of proteins, carbohydrates, lipids and nucleic acids, **zinc can have a catalytic or structural function, its deficiency being able to cause reduced carbonic anhydrase, disturbances of the palate (dysgeusia and hypogeusia) and xerostomia**[58,59].

Zinc is also essential to the normal function of the immunological system, its deficiency being able to lead to thymic atrophy, lymphopenia, reduction of immunoglobulin mitosis, among other alterations. Damage also occurs in the mucous barrier of the gastrointestinal and pulmonary tract. The oxidative stress has often been related to the phases of initiation and promotion of the process of carcinogenesis. The antioxidant enzymes, dependent upon selenium and zinc, which antagonize this process, are at low levels in the tumor cells[60, 61].

Study done by McMillan et al [62] corroborated such data, when it was noted that concentrations of plasmatic zinc of patients with gastrointestinal cancer were significantly lower when compared with healthy individuals.

Such data indicates the importance of offering daily the recommendation of this mineral in oncological patients.

The daily dose of **IMMAX provides 135% of RDI* of ZINC.**

99,5% of RDA** **for men.**

112% of RDA** **for women.**

*RDI - Recommended Daily Ingestion
**RDA - Recommended Dietary Allowances

NUTRIENTS	IDR	100ml	154g | 630kcal	% IDR*
Proteins (g)	50	6,2	39,4	79
Calcium (mg)	1000	88	554	55
Ferro (mg)	14	0,91	5,7	41
Vitamin A (mcgRE)	600	88	558	93
Vitamin D (mcg)	5	0,93	5,9	117
Vitamin B1 (mg)	1,2	0,11	0,7	58
Vitamin B2 (mg)	1,3	0,12	0,8	58
Nicotinamide (mg)	16	1,5	9,5	59
Pantothenic Acid (mg)	5	0,47	3,0	59
Vitamin B6 (mg)	1,3	0,16	1,0	77
Vitamin B12 (mcg)	2,4	0,22	1,4	58
Vitamin C (mg)	45	14	87	193
Vitamin E (mg)	10	1,4	8,8	88
Biotin (mcg)	30	2,8	18	59
Folic Acid (mcg)	240	30	188	78
Vitamin K (mcg)	65	11	71	110
Phosphorous (mg)	700	63	399	57
Magnesium (mg)	260	23	147	57
Zinc (mg)	7	1,5	9,4	135
Copper (mcg)	900	83	523	58
Iodine (mcg)	130	14	87	67
Selenium (mcg)	34	10	63	185
Molybdenum (mcg)	45	4,2	26	59
Chrome (mcg)	35	3,3	21	59
Manganese (mg)	2,3	0,21	1,3	57
Choline (mg)	500	29	186	37

Osmolarity: 390 mOsm/L H_2O

TABLE 3: *Nutritional information of proteins, micronutrients and and RDI % in a dose of IMMAX.*

RECOMMENDED DAILY DOSE OF IMMAX

The standard dose indicated for daily consumption of IMMAX corresponds to 154 g/day, or 18 measuring spoons.

The daily portion offers 630 calories, offering 39.4 grams of protein (namely 7.2 grams of L-leucine), besides prebiotic food fiber (9.4 grams). It provides about 77% of the recommended daily ingestion of vitamins and minerals.

VERSATILITY IN THE PREPARATION OF ADHESION TO IMMAX

An important point to be considered on the indication of oral nutritional therapy is the adhesion of the patient to the treatment proposed. Among the factors which can be associated with the low adhesion to the oral nutritional supplement is the monotony of the taste of the product indicated, the palatability being a key factor in its acceptance[63]. Thus, the importance of monitoring and guidance by health professionals to ensure adhesion and obtain results favorable to the patient's evolution.

As it is an unflavoured product, IMMAX can be added to any type of preparation, hot or cold, sweet or salty, thereby allowing greater versatility in its means of presentation.

Its recommended daily dose can be fractionized throughout the day, in all the means, as per the patient's requirement and tolerance, allowing individualization of the treatment and greater adhesion thereto.

TABLE 4: *Nutritional Recommendation X Calculated Estimate X IMMAX*[17, 23, 25, 47, 64, 65, 66, 67]

	Nutritional Recommendation	Estimate of Consumption (Adult 60 kg)	IMMAX
Calories	**Weight maintenance:** 20 – 30 kcal/kg/day **Weight gain:** 30 – 35 kcal/kg/day	1500 – 2100 kcal/day **Avg** = 1800 kcal/day 35% = 630 kcal	**630 kcal = 154g**
Proteins	1 a 2g/kg/dia	60 - 120g/day **Avg** = 90g/day 35% = 31,5g	**39,4g (44%)**
L-leucine	**RDA:** 0,042 to 0,052g/kg/day **Studies:** Muscular mass increase 1,7 to 2,8g/meal	2,52 – 3,12g/day **Avg** = 2,82g/day 35% = 0,99g UL* = 35g	**7,2g**
Fibers	15 to 30g/day 5 to 10g prebiotic fiber/day	35% = 7,8g 2,6g prebiotic	**9,4g prebiotic fiber (42%)**
Micronut.	RDI: 1 to 2x/day **RDA:** 1x/day	35% to 70% RDI and RDA	**77% RDI 78% RDA**

**UL - Upper Limit*

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