

Impact of High Vitamin C Intakes on the Development of Digestive Cancers

SOUALEM-MAMI Zoubida^{1*}, GHANEMI Fatima Zohra², BENGHALEM Nouha³, BENYAHIA Chahrazed², KACHEKOUICHE Youcef²

¹Natural Products Laboratory (LAPRONA), Department of Biology, Faculty of SNV/STU, Tlemcen University (Algeria)

Email: zoubida.mami@univ-tlemcen.dz

²Natural Products Laboratory (LAPRONA), Department of Biology, Faculty of SNV/STU, Tlemcen University (Algeria)

³Epidemiologist doctor, EPH Nedroma, Tlemcen(Algeria)

Abstract

Digestive cancer is a major public health problem with discreet and insidious evolution until the appearance of serious consequences in terms of morbidity and mortality. This work aims to demonstrate the impact of a diet rich in ascorbic acid on the evolution of digestive cancer. A descriptive observational study was carried out over a period of 3 months, for 30 patients with digestive cancer selected at the hospitals of Tlemcen, Nedroma and Ghazaouet, where a questionnaire was conducted. A diet was proposed, and a vitamin C dosage was carried out on the plasma of the patients before and after the introduction of this diet. Tumor locations were associated with fruits and vegetables consumption ($p=0.016$). In addition, the vitamin C mean after the diet was significantly higher than before the diet ($p<0.0001$), and there was a significant association between the improvement of patients' health and the vitamin C-rich diet ($p<0.0001$), with a decrease in the effects of chemotherapy (39.13 %) or even a stabilization (34.78 %). Also, an improvement in the health status of the cancer patients (26.09 %) has been shown. In order to target preventive actions against digestive cancer, a better knowledge of the lifestyle of cancer patients, combined with a balanced diet supplemented with vitamin C, and a restriction of foods that acidify the blood pH is highly recommended.

Keywords: digestive cancer, adequate diet, vitamin C, supplementation.

1. Introduction

Cancer is a major public health problem. Its control has become one of the health strategies of governments around the world (Liu et al., 2021). Generally, cancer represents the second leading cause of death, with approximately 10 million cancer deaths recorded in 2020 (Ferlay et al., 2021).

Around one-third of cancer deaths are due to tobacco use, high body mass index, alcohol use, low fruit and vegetable intake, and lack of physical activity (WHO and FAO, 2021). Effectively, the most common cases (in terms of new cancer cases) in 2020 were breast (2.26 million cases), lung (2.21 million cases) and colorectal (1.93 million cases), while the most common causes of cancer deaths in the same year were: lung (1.80 million deaths), colon and rectum (935 000 deaths) and liver (830 000 deaths) (WHO, 2020). According to the World Cancer Research Fund with that of the reference of 2018, 18 million new cases were diagnosed. Globally, a higher incidence of lung and breast cancer (12.3% in both cases) was registered, followed by a higher incidence of colorectal cancer (10.6%), prostate cancer (7.5%), stomach cancer (6.1%) and liver cancer (5.0%) (Bray et al., 2018).

The literature review also showed that regular consumption of fruits and vegetables rich in fiber (e.g. whole grains) and vitamins with a low intake of meat, and a moderate intake of milk, dairy, and alcohol might be considered as an optimal

combination in the prevention of cancer. These recommendations in combination with the healthier dietary patterns are proposed as emerging medical prescription (Lăcătușu et al., 2019).

In Algeria the available data from the World Health Organization, show that cancer accounted for 21% of the causes of mortality and the rate of new cases in 2015 reached 45,000 (WHO, 2014). The national average crude cancer incidence rate was 112.2 new cases per 100,000. It was much higher for women (131.7 new cases per 100,000) than men (93.7 new cases per 100,000). Female breast cancer is the most common of all cancers in all Wilayas, with 4934 new cases. Moreover, colorectal cancer is the 1st cancer for men and the 2nd cancer for women. This cancer is growing rapidly: + 3.7% per year. Prostate cancer is also the third most common cancer for men (Hammouda and Boutekdjiret, 2020). In 2018, colorectal cancer (CRC) rates in Algeria ranked in the first place among the North African countries, with about 3000 deaths and more than 5500 new cases. Nonetheless, the incidence of CRC in Algeria is lower than that of many Mediterranean countries in Southern Europe (Bray et al., 2018). Approximately 50% of digestive cancers are located in the second rank. Stomach cancer is located in the fifth rank, with 25% of the cases are men and 17.5% are women as well as cancers of the extra hepatic bile ducts (Abid, 2016). The

Wilaya of Tlemcen has counted 785 deaths between 2012 and 2017, 414 cases with a percentage of 54.7% for men and 343 for women with a percentage of 45.3% (University Hospital Center, 2018; Berber, 2018).

One of the most important risks of cancer development consists in improper diet, which contains high amount of processed foods and high sugar levels, all potentially acting as malignant drivers. However, it has been established by some studies that several nutrients or specific dietary components are able to decrease the possibility of malignant cell transformation or to inhibit the growth and the spread of pre-existing malignant masses (Chen et al., 2015; Gulei et al., 2018). Besides, the epidemiology of gastrointestinal cancer suggests that the most important factor is the lack of detoxifying protective factors rather than the excess of harmful factors (Nielsen, et al., 2015). Fortunately, the list of nutrients that could exert an inhibitory effect on cancer development is fairly extensive, with evidence in the scientific literature. The administration of these nutrients showed significant results *in vitro* and *in vivo* toward cancer inhibition (Irimie et al., 2019). Among the popular vitamins that are largely available in natural fruit or supplement form, the vitamin C or the ascorbic acid is the best known and the most consumed. Plasma vitamin C concentrations in cancer patients were significantly reduced compared to healthy controls; which raising several questions about cancer and vitamin C involvement (Chen et al., 2015). To neutralize the progression of a malignant tumor mass, vitamin C can be administered for its dose-dependent anti-carcinogenic properties (Verrax et Calderon, 2008). The testified dose-dependent of vitamin C are also specific to cancer type, for example in melanoma, low doses induced cell proliferation, whereas higher doses of vitamin C triggered apoptosis (Mastrangelo et al., 2018; Mustafi et al., 2018).

However, higher doses of vitamin C can induce an anti-cancer effect via the generation of hydrogen peroxide and superoxide anion radicals in case of human tongue carcinoma cells (Ohwada et al., 2017). Numerous studies have illustrated the beneficial effects of vitamin C in cancer using the concept of micronutrient synergies, which support the efficacy of vitamin C in targeting anti-cancer mechanisms with high consumption of cooked and especially raw fruits and vegetables. Carbohydrates (white sugar) should also be limited, as they interfere with the absorption of this vitamin and deplete it in the white blood cells, making them sluggish (Irimie et al., 2019). Overall, vitamin C acts as an anti-cancer agent, destroying free radicals. It also helps to strengthen connective tissue, inhibit the growth of cancer cells, induce their natural death, allows organs to repair damage and regulate cellular functions (Verrax and Calderon, 2008).

The aim of this study is to determine the effect of balanced diet supplemented with vitamin C on the evolution of digestive cancer and on the lifestyle of cancer patients.

2. Material and Methods

Study Population

Thirty patients with digestive cancers from 03 hospitals (Tlemcen, Ghazaouet, and Nedroma) were selected between February and may of the year 2018, to participate in a descriptive observational study. After taking the institutional ethics committee clearance, patients were interviewed using a questionnaire at the oncology department (patients undergoing chemotherapy) during a diagnostic examination or at home (patients at an advanced stage), the parameters collected for each patient are age, sex, BMI, socioeconomic level, profession, education level, family status, tumor locations, daily intake of fruits and vegetables and the intake of processed foods. In addition, blood samples of 5 mL were taken in heparin tubes for the measurement of vitamin C.

Vitamin C Diet Composition

During 3 months of the study, a diet rich in vitamin C was proposed. The choice of diet was based on its richness in foods rich in vitamin C and which are traditionally consumed for the prevention and treatment of cancer. Four diet compositions were prepared; the first diet was composed of 3 lemons, 1 onion, 3 cloves of garlic, 4 g of ginger, and 150 g of honey. The second diet composition is 250 g of beetroot, 200 g of carrot, 150 g of zucchini, 100 g of radish, 100 g of parsley, and 100 g of potato. The third one was composed of 7 lemons, 7 cloves of garlic, 200 g of nuts, 200 g of wheat germ, and 200 g of honey. Patients consumed all three diets each day for four meals. The fourth diet composition is flour, which contains 200 g of 7 seeds including wheat, chickpeas, white beans, lentils, flaxseed, dried beans, and sweet almond. This flour was consumed every day between meals.

Determination of Ascorbic Acid

Many methods are available for the determination of plasma vitamin C (ascorbic acid). The method of Jagota and Dani (1982), which is the one used in the present study. This colorimetric technique uses Folin reagent and a standard range of ascorbic acid. After precipitation of plasma proteins by trichloroacetic acid and centrifugation, the supernatant is mixed with distilled water and Folin reagent. The vitamin C present in the supernatant reduces the Folin reagent with yellow coloration shown. The intensity of the coloration obtained is proportional to the concentration of vitamin C present in the sample with an absorbance at 520 nm. The concentration is determined from a standard curve obtained from a stock of ascorbic acid solutions (Jagota and Dani, 1982).

Statistical Analysis

Results are expressed in percentages (%), in mean and range for age. Chi-square and Fisher's exact test were used to determine the different associations. Student test was performed to compare vitamin C means.

All statistical analysis were performed using IBM SPSS version 23 software. The results were considered statistically significant at $p < 0.05$.

3. Results

Table 1. Anthropometric, socioeconomic, clinicopathological, and nutritional characteristics of the studied population.	
Different markers	Number
Age	54.63
Mean	20 to 80
Range	
Sex	
• Men	14 (46.7%)
• Women	16 (53.3%)
BMI	
• Undernourished	6 (20%)
• Lean	18 (60%)
• Normal	6 (20%)
Socioeconomic level	
• Low	13 (43.4%)
• Medium	13 (43.4%)
• High	4 (13.3%)
Profession	
• without profession	20 (66.7%)
• With profession	8 (26.6%)
• pensioner	2 (6.7%)
Education level	
• Illiterate	9 (30%)
• Middle	16 (53.3%)
• Higher	5 (16.7%)
Family status	
• Single	2 (6.7%)
• Divorced	4 (13.3%)
• Married	23 (76.7%)
• Widowed	1 (3.3%)
Tumor locations	
• Aero-digestive	3 (10%)
• Gastric	13 (43.33%)
• Hepatic	3 (10%)
• Esophagus	1 (3.33%)
• Colorectal	10 (33.33%)
Portion % consumed of fruits and vegetables per day	
• 25	21 (70%)
• 50	5 (16.7%)
• 75	4 (13.3%)
Portion % consumed of processed foods per day	
• 25	5 (16.7%)
• 50	15 (50%)
• 75	10 (33.3%)

In table 1, the mean age of the patients was 54.63 years, with extremes of 20 to 80 years. It was noted in this study that the percentage of women was (53.3 %) higher than that of men (46.7 %). However, this variation remains more or less negligible. 20 % of the cases are of normal weight, 20 % are undernourished and 60% of the cases are thin. All the patients included are underweight.

More than 2/3 of the patients have a medium (43.4 %) or low (43.4%) socio-economic level, which may explain the lack of a culture of a healthy lifestyle with good nutrition, and which could be an obstacle to the application of an adequate diet to strengthen the therapeutic management of patients. Results

obtained show that patients have an overall low socioeconomic level due to the absence of a regular job, of which 66.7 % of patients are without a stable profession. About half of the patients have a middle education level (53.3 %), whereas 30 % are illiterates and 16.7 % have a higher education level. The majority of patients (76.7 %) are married, and few are divorced, single or widowed.

Five tumor locations were observed, 43.33% of the patients have a gastric tumor and 33.33 % have a colorectal tumor, against 10 % of the patients with aero-digestive and hepatic tumors, and only 3.33 % of the patients with esophagus tumor.

Table 2. Association between tumor locations and age, sex, fruits and vegetable consumption, and processed foods consumption.

Parameters	Aero-digestive	Gastric	Hepatic	Esophagus	colorectal	p-value
Age						
≤50	1 (33.33%)	4(30.77%)	1 (33.33%)	1 (100%)	1 (10%)	0,352
>50	2 (66.67%)	9(69.23%)	2 (66.67%)	0 (0%)	9 (90%)	
Sex						
Men	1 (33.33%)	5(38.45%)	1 (33,33%)	0 (0%)	7 (70%)	0,428
Women	2 (66.67%)	8(61,54%)	2 (66,67%)	1 (100%)	3 (30%)	
Fruits and vegetables consumption (portion %)						
25	2 (66.67%)	13 (100%)	1 (33.33%)	1 (100%)	6 (60%)	0.016
50	1 (33.33%)	0 (0%)	0 (0%)	0 (0%)	3 (30%)	
75	0 (0%)	0 (0%)	2 (66.67%)	0 (0%)	1 (10%)	
Processed foods consumption (portion %)						
25	0 (0%)	5(38.46%)	2 (66,67%)	0 (0%)	4 (40%)	0,159
50	0 (0%)	5(38.46%)	1 (33.33%)	1 (100%)	4 (40%)	
75	3 (100%)	3(23,08%)	0 (0%)	0 (0%)	2 (20%)	

25, 50, 75 represent a portion %

Table 2 shows that 70 % of the patients consume a low quantity of fruits and vegetables, however, 16.7 % and 13.3 % consume a medium and higher quantity of fruits and vegetables. The frequency of

consumption of processed foods is higher (50 %) for the half of the cancer subjects, whereas 33.3 % and 16.7 % of these patients consume 75 % and 25 % of this type of food, respectively.

Table 3. Association between vitamin C status after diet and age, sex, and cancer locations

Parameters	Hypovitaminose	Normal	p-value
Age			
≤50	6 (42,86%)	2 (12,50%)	0.101
>50	8 (57,14%)	14 (87,50%)	
Sex			
Men	5 (35,71%)	9 (56,25%)	0,299
Women	9 (64,29%)	7 (43,75%)	
Tumor locations			
Aero-digestive	1 (33,33%)	2 (66,67%)	0,806
Gastric	7 (53,85%)	6 (46,15%)	
Hepatic	1 (33,33%)	2 (66,67%)	
Esophagus	0 (0%)	1 (100%)	
Colorectal	5 (50%)	5 (50%)	

Tumor locations including aero-digestive, gastric, Esophagus, and colorectal were significantly associated with lower fruits and vegetable consumption (p= 0.016), unlike hepatic cancer.

Furthermore, no significant associations were found between tumor location and age (p= 0.352), sex (p= 0.428), and processed foods consumption (p= 0.159)(Table.3).

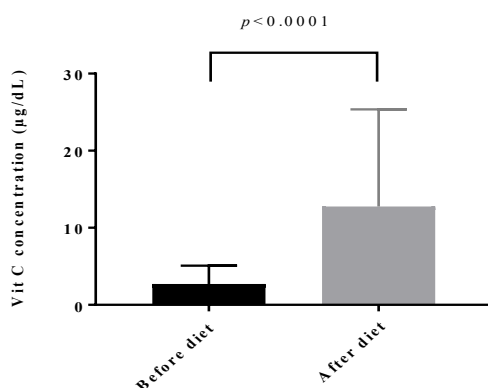


Figure1. Concentrations of vitamin C before and after the diet.

Figure 1 shows a great variability in the concentration of vitamin C before and after the diet. A significant

difference ($p < 0.0001$) was observed in the means, with a value of $2.71 \pm 2.36 \mu\text{g/dL}$ before diet against $12.77 \pm 12.60 \mu\text{g/dL}$ after diet.

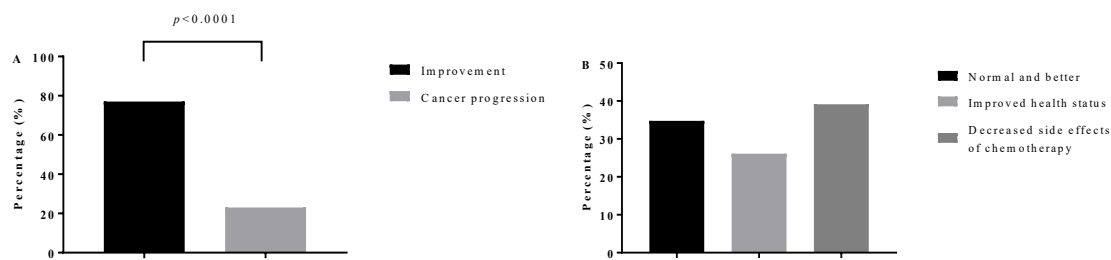


Figure 2. Evolution of the status of cancer patients supplemented with a vitamin C-rich diet

In figure 2, improvement of cancer conditions in patients was significantly associated with a vitamin C supplement diet ($p < 0.0001$). In addition, 39.13 % of patients showed a decrease in side effects of chemotherapy, stable and better cases (34.78 %), with also an improvement in health status (26.09 %).

4. Discussion

It is well known that vitamin C plays a crucial role in many vital processes, as a protective agent against excess of reactive oxygen species, gene expression control and maintenance of iron homeostasis. Consequently, even a moderate deficiency can have severe health consequences (Salganik, 2001; Young et al., 2015).

This can certainly be avoided by adjustment and/or adequate supplementation in the diet. Excess of vitamin C is however safe because kidneys remove it to prevent a possible overdose (Łukawski et al., 2020). The recommended daily intake of vitamin C for a healthy person is 500 mg/day (Paschalis et al., 2016). Several studies have shown that it is favorable to increase this dose of vitamin C during oncological therapies periods (Du et al., 2012; Fritz et al., 2014), in the treatment of skin diseases (Kishimoto et al., 2013), in the reduction of stroke effects (Spector, 2016), or in the elimination of some disorders of the digestive system (Aditi and Graham, 2012).

Vitamin C is a six-carbon ketolactone synthesized from glucose by most animals in the kidney or the liver (Padayatty and Levine 2016). However, humans as well as other primates, guinea pigs and fruit bats, are unable to synthesize vitamin C because they harbor inactivating mutations in the gene encoding L-gulonolactone oxidase (GULO), the enzyme responsible for catalyzing the last step of vitamin C synthesis. Humans must therefore acquire vitamin C from dietary sources (Maeda et al., 2000; Ngo et al., 2019).

Vitamin C has long been known to be involved in oxidative stress. Indeed, this vitamin has an effect on apoptosis through the regulation of a known anti-apoptotic protein represented by Bcl-2 (Azad et al., 2010). Apart from the contribution of vitamin C in oxidative stress, it has been shown that this active molecule inhibits the formation of N-nitrosamine carcinogenic compounds (Hecht, 1997) and

Moreover, vitamin C status after diet was independent of age ($p = 0.101$), sex ($p = 0.299$), and tumor locations ($p = 0.806$).

modulates effectively the immune response [Carr and Frei, 1999]. Furthermore, epidemiological studies revealed that vitamin C could reduce the risk of malignancies (Chi et al., 2015; Saman, 2012).

It should also be noted that the beneficial effects of vitamin C is linked to the beneficial effects of a healthy diet rich in fruits or vegetables (Saman, 2012; Kune et al., 1993).

One of the above-mentioned anti-carcinogenic properties attributed to Vitamin C is sensitivity to chemotherapy (Nasu et al., 2011). Another anti-carcinogenic property comes from its function as an anti-oxidant, ascorbic acid producing small amounts of hydrogen peroxide. The amount of hydrogen peroxide generated from high doses of Vitamin C can be lethal to cancer cells due to their low quantities of hydrogen peroxide-processing enzymatic and non-enzymatic mechanisms. The eventual lysis of cancer cells is caused by the accumulation of hydrogen peroxide through the induction of apoptosis (Chen et al., 2015; Verrax and Calderon, 2008).

Othman et al. identified frequently consumed foods by patients (red meats, black tea, meats, offal, frying, and sweets) compared to controls (green tea, fruits, and cereals which are CRC protective food). They concluded that malnutrition was very common in patients with CRC with serious vitamin and mineral deficits (Othman et al., 2018).

The aim of the present work was to investigate the effect of vitamin C on colorectal cancer. Thirty cases of cancer diagnosed based on the histological evidence were included in this study and a healthy diet supplemented with vitamin C was prescribed for these patients. The average age was 53.63 years with a standard deviation of 13.586. The sex ratio was 1.14 with a slight of male predominance. Most patients have a certain belief and habits of cultural origin that may influence the choice of their food. Indeed, it was perceived in these patients a conviction that the diet has no effect on their health. Almost 66.7 % of patients had no real profession, two thirds were married and their socio-economic level was low (43.3 %).

These findings are in adequacy with those of the study conducted by Negrichi and Taleb, which identifies the risk factors for CRC in Algeria,

especially in the eastern region (Negrichi and Taleb ,2021). Indeed, the results of this study revealed a significant association between higher educational level and a decreased risk of CRC. Furthermore, the hereditary factor of cancer in general increases the risk of CRC. Diagnosis of any cancer or of CRC in first, in second- or in third-degree relatives also was significantly related to CRC risk. In the same way, occupational exposures showed a significant association with an increased risk of CRC, as did obesity, alcohol consumption, and passive smoking.

In all patients of this study, we noticed a desire to find alternative methods such as herbs and other nutrients in hopes of curing their disease because the current treatment they were taking did not bring great results. After understanding the objectives of the present work, and the fact that the human organism is biologically programmed to consume large amounts of plants, mainly fruits and vegetables, patients were convinced to follow a diet based on fruits and vegetables. The minimum recommended intake is five servings of fruits and vegetables per day, which corresponds to about 400 grams of vegetables and 250 grams of fruits (WHO and FAO, 2019).

Many studies have shown that vitamin C has an influence on cancer diseases in general and on the digestive tract in particular as well as the drug treatments (from chemotherapies and radiotherapies), by increasing the needs of ascorbic acid (vitamin C) contained in fruits and vegetables (Ngo et al., 2019; Vissers and Das , 2018;Takahashi et al., 2012).

A recent published data on critically ill patients (n = 44, both septic and no septic patients) shows that actual plasma vitamin C concentrations are on average 60 % lower than the values predicted from vitamin C intake for patient during hospitalization (either enteral or parenterally administered nutrition) (Carr et al., 2017). Although interactions with administered care and therapeutics may affect vitamin C bioavailability, these data suggest significant alterations in the pharmacokinetics of vitamin C in this group of patients, reflected by the difference in the almost linear course of the plasma concentration curve opposed to the predicted increase over time (Lykkesfeldt and Tveden-Nyborg 2019). It remains to be determined whether restoring normal vitamin C status in critically ill patients has a clinically significant impact on disease prognosis, or is it just that promising results are emerging (Marik et al., 2017).

A very recent meta-analysis suggests that vitamin C therapy significantly shortens the stay of patients in the intensive care unit (Hill et al., 2019). Regarding the intake of vitamin C in food, patients who underwent surgery and followed their diet, have an increase in plasma vitamin C levels, while their health stabilized, their medical control showed no abnormalities, and their quality of life had become better. These results are in agreement with those of Fukushima and Yamazaki, (2010); Blass et al. (2012) and Cereda et al. (2009).

On the other hand, patients who did not follow the fruit and vegetable diet still suffered from hypovitaminosis C, a very low level of vitamin C in the plasma, a progression of the disease and an imbalance in the biological parameters (CBC, creatinine, bilirubin). Processed foods may therefore be possible risk factors for digestive cancer.

In non-metastatic patients who did not respond to conventional treatments (radiotherapy, chemotherapy), and who followed the diet and the restriction of sugars (which impair the absorption of vitamin C and animal proteins that acidify the pH of the body), it was noticed that the cancers decreased in size on MRI.

De Francesco et al. (2017) suggested that Vitamin C's action as a glycolytic inhibitor may represent an effective and safe strategy to be used in combination therapies, with conventional anticancer drugs.

In subjects, who well followed the diet and were undergoing chemo/ radiation therapy, vitamin C in that case has more or less reduced the side effects of chemotherapy (nausea and vomiting, loss of appetite, hair loss, mouth sores, lowered red blood cell count and tiredness).

This significant difference in diet observed in the studied population is due to the very unbalanced diet related to an unhealthy lifestyle and poor socio-economic conditions. To correct this situation, a balanced diet rich in fruits and vegetables, together with an adequate lifestyle, allow reaching the recommended daily intake, which is sufficient to avoid the consequences and to prevent diseases, including cancer.

Furthermore, it has been shown that vitamin C can affect cell survival by stabilizing p53, the main controller of cell proliferation and apoptosis. This vital vitamin has also been recognized for its protection against radiation-induced cell damage (Kaźmierczak-Barańska et al., 2020).

Last but not least, Mehdad et al. (2020) suggest that following a strict diet higher in plant foods such as vegetables, fruits and whole grains while avoiding high red and processed meats, fat and refined carbohydrates, limiting alcohol consumption, keeping a healthy weight, and engaging in regular physical activity are crucial for cancer prevention interventions. Several studies have also demonstrated a strong and inverse relationship between a high level of Mediterranean diet adherence and some chronic diseases (such as diabetes, cardiovascular diseases etc.) and cancer (Mentella et al., 2019).

5. Conclusion

Vitamin C is a versatile substance that supports many aspects of the body. It is therefore one of the most important vitamins for health and life.

Results obtained show that all the subjects surveyed had hypovitaminosis C before the introduction of the diet, show a significant difference between the vitamin C dosage in cancer patients before and after diet ($p < 0.0001$), with a stabilization or even an improvement of the health status of cancer patients

over a period of 3 months ($p < 0.0001$).

All these results prove that the dosage of vitamin C should be prescribed more often for any patient, in particular in cancerology. The determination of vitamin C should therefore be systematically a part of the biological assessment of cancer patients.

Emphasis must also be placed on a diet closer to that of our ancestors, rich in vitamins and various bioactive elements, which allows the body to drain its pollution by purifying the vital space of the cells and ensuring a self-regeneration of these cells.

6. Acknowledgments

The authors thank the substantial work of the volunteer team of the Oncology department, Tlemcen Hospital, University of Tlemcen. Algeria.

7. Author's Contributions

SMZ and BN co-supervised the conduct of the study and performed the analysis of the prepared diets. BCH conducted the recruitment and data collection. GFZ and KY performed statistical analyzes and prepared tables and figures. Statistical analysis supervised by BN. BM was responsible for the design of the study. All authors have read and approved the submitted manuscript.

Disclosure statement

The authors reported no potential conflict of interest.

8. Funding

The Natural Products Laboratory (LAPRONA), Tlemcen University, supported this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

Liu Z, Liao Z, Chen Y, et al (2021) Research on CRISPR/system in major cancers and its potential in cancer treatments. *Clin Tranl Oncol*; 23: 425-433. <https://doi.org/10.1007/s12094-020-02450-3>

Ferlay J, Colombet M, Soerjomataram I, et al (2021) Cancer statistics for the year 2020: An overview. *Int J Cancer*. <https://doi.org/10.1002/ijc.33588>

World Health Organization (WHO)/Food and Agriculture Organization (FAO) of the United Nations. <https://gicr.iarc.fr/about-the-gicr/the-value-of-cancer-data/>, accessed February 2021

WHO, 2020.

Bray F, Ferlay J, Soerjomataram I, et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA cancer J Clin*; 68: 394-424. <https://doi.org/10.3322/caac.21492>

Lăcătușu CM, Grigorescu ED, Floria M, et al (2019). The mediterranean diet: From an environment-driven food culture to an emerging medical prescription. *Int J Environ Res Public Health*; 16: 942. <https://doi.org/10.3390/ijerph16060942>

WHO, 2014.

Hammouda D, Boutekdjiret L (2020). Surveillance épidémiologique des cancers: Résultats préliminaires nationaux. *AJHS*; 2: 32-41.

Abid L. Épidémiologie du cancer digestif en Algérie. *ffcd-sahgeed* 2016 September [accessed 2018 May 2021].

https://www.sahgeed.com/upload/files/1stAIBDD2016/Epidemiologie_des_cancers_digetifs_en%20Algerie.pdf

University Hospital Center. Cancer registry of Tlemcen. 2018. Department of Epidemiology and Preventive Medicine.

Berber N (2018) Service de médecine nucléaire. CHU de Tlemcen. réperé à [http://toutsurtlemcen.in\(consulte\)](http://toutsurtlemcen.in(consulte))

Chen Q, Polireddy K, Chen P, et al (2015) The unpaved journey of vitamin C in cancer treatment. *Can J physiol pharmacol*; 93: 1055-1063. <https://doi.org/10.1139/cjpp-2014-0509>

Gulei D, Petrut B, Tigu AB et al (2018) Exosomes at a glance—common nominators for cancer hallmarks and novel diagnosis tools. *Crit Rev Biochem Mol Boil*; 53: 564-577.

<https://doi.org/10.1080/10409238.2018.1508276>

Nielsen, TK, Højgaard M, Andersen JT, et al (2015) Elimination of Ascorbic Acid After High-Dose Infusion in Prostate Cancer Patients: A Pharmacokinetic Evaluation. *Basic Clin Pharmacol Toxicol*; 116: 343-348. <https://doi.org/10.1111/bcpt.12323>

Irimie AI, Braicu C, Pasca S, et al (2019) Role of key micronutrients from nutrigenetic and nutrigenomic perspectives in cancer prevention. *Medicina*; 55: 283. <https://doi.org/10.3390/medicina55060283>

Verrax, J, Calderon, PB (2008) The controversial place of vitamin C in cancer treatment. *Biochem Pharmacol*; 76: 1644-1652. <https://doi.org/10.1016/j.bcp.2008.09.024>

Mastrangelo D, Pelosi E, Castelli G, et al (2018) Mechanisms of anti-cancer effects of ascorbate: Cytotoxic activity and epigenetic modulation. *Blood Cells Mol Dis*; 69: 57-64. <https://doi.org/10.1016/j.bcmd.2017.09.005>

Mustafi S, Camarena V, Volmar CH, et al (2018) Vitamin C sensitizes melanoma to BET inhibitors. *Cancer Res*; 78: 572-583. <https://doi.org/10.1158/0008-5472.CAN-17-2040>

Ohwada R, Ozeki Y, Saitoh Y (2017) High-dose ascorbic acid induces carcinostatic effects through hydrogen peroxide and superoxide anion radical generation-induced cell death and growth arrest in human tongue carcinoma cells. *Free Radic Res*; 51: 684-692.

<https://doi.org/10.1080/10715762.2017.1361533>

Jagota SK, Dani HM. (1982) A new colorimetric technique for the estimation of vitamin C using Folin phenol reagent. *Anal Biochem*; 127: 178-182.

Salganik RI (2001) The benefits and hazards of antioxidants: controlling apoptosis and other protective mechanisms in cancer patients and the human population. *J Am coll nutr*; 20(sup5): 464S-472S.

<https://doi.org/10.1080/07315724.2001.10719185>

Young JI, Züchner S, Wang G (2015) Regulation of the epigenome by vitamin C. *Annu Rev Nutr*; 35: 545-564.

<https://doi.org/10.1146/annurev-nutr-071714-034228>

Łukawski M, Dalek P, Borowik T, et al (2020) New oral liposomal vitamin C formulation: Properties and bioavailability. *J Liposome Res*; 30: 227-234.

<https://doi.org/10.1080/08982104.2019.1630642>

Paschalis V, Theodorou AA, Kyparos A, et al (2016) Low vitamin C values are linked with decreased physical performance and increased oxidative stress: reversal by vitamin C supplementation. *Eur J Nutr*; 55: 45-53. <https://doi.org/10.1007/s00394-014-0821-x>

Du J, Cullen JJ, Buettner GR (2012) Ascorbic acid: chemistry, biology and the treatment of cancer. *Biochim Biophys Acta - Rev Cancer*; 1826: 443-457.

<https://doi.org/10.1016/j.bbcan.2012.06.003>

Fritz H, Flower G, Weeks L, et al (2014) Intravenous vitamin C and cancer: a systematic review. *Integr Cancer Ther*; 13: 280-300.

<https://doi.org/10.1177/1534735414534463>

Kishimoto Y, Saito N, Kurita K, et al (2013) Ascorbic acid enhances the expression of type 1 and type 4 collagen and SVCT2 in cultured human skin fibroblasts. *Biochem Biophys Res Commun*; 430: 579-584. <https://doi.org/10.1016/j.bbrc.2012.11.110>

Spector R (2016) Dehydroascorbic acid for the treatment of acute ischemic stroke. *Med hypotheses*; 89: 32-36. <https://doi.org/10.1016/j.mehy.2016.01.021>

Aditi A, Graham DY (2012) Vitamin C, gastritis, and gastric disease: a historical review and update. *Dig Dis Sci*; 57: 2504-2515. <https://doi.org/10.1007/s10620-012-2203-7>

Padayatty SJ, Levine M. (2016) Vitamin C: the known and the unknown and Goldilocks. *Oral dis*; 22: 463-493. <https://doi.org/10.1111/odi.12446>

Maeda N, Hagihara H, Nakata Y, et al (2000). Aortic wall damage in mice unable to synthesize ascorbic acid. *Proc Natl Acad Sci*; 97: 841-846. <https://doi.org/10.1073/pnas.97.2.841>

Ngo B, Van Riper JM, Cantley LC, et al (2019). Targeting cancer vulnerabilities with high-dose vitamin C. *Nat Rev Cancer*; 19: 271-282. <https://doi.org/10.1038/s41568-019-0135-7>

Azad N, Iyer A, Vallyathan V, et al (2010) Role of oxidative/nitrosative stress-mediated Bcl-2 regulation in apoptosis and malignant transformation. *Ann N Y Acad Sci*; 1203: 1-6. <https://doi.org/10.1111/j.1749-6632.2010.05608.x>

Hecht SS (1997). Approaches to cancer prevention based on an understanding of N-nitrosamine carcinogenesis. *Proc Soc Exp Biol Med*; 216: 181-191. <https://doi.org/10.3181/00379727-216-44168>

Carr AC, Frei B (1999) Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. *Am J Clin Nutr*; 69:1086-1107.

<https://doi.org/10.1093/ajcn/69.6.1086>

Chi AC, Day TA, Neville BW (2015) Oral cavity and oropharyngeal squamous cell carcinoma—an update. *CA Cancer J Clin*; 65: 401-421. <https://doi.org/10.3322/caac.21293>

Saman DM (2012) A review of the epidemiology of

oral and pharyngeal carcinoma: update. *Head Neck Oncol*; 4: 1-7. <https://doi.org/10.1186/1758-3284-4-1>

Kune GA, Kune S, Field B, et al (1993) Oral and pharyngeal cancer, diet, smoking, alcohol, and serum vitamin a and β -carotene levels: A case-control study in men. *Nutr Cancer*; 20: 61–70.

<https://doi.org/10.1080/01635589309514271>

Nasu K, Kawano Y, Tsukamoto Y, et al (2011) Aberrant DNA methylation status of endometriosis: epigenetics as the pathogenesis, biomarker and therapeutic target. *J Obstet Gynaecol Res*; 37: 683-695.

<https://doi.org/10.1111/j.1447-0756.2011.01663.x>

Othman RB, Ksira I, Smida A, et al (2018) Malnutrition and risk factors in tunisian patients with colorectal cancer. *IJMBS*; 10: 88.

<http://www.ijmbs.org/text.asp?2018/10/3/88/233763>

Negrichi S, Taleb S (2021) Hereditary, environmental, and dietary risk factors of colorectal cancer: a case-control study in the Algerian East. *Environ Sci Pollut Res*; 28: 12372-12381. <https://doi.org/10.1007/s11356-020-10378-y>

World Health Organization, Food and Agriculture Organization of the United Nations. Diet, Nutrition and the Prevention of Chronic Diseases. Geneva. WHO Technical Report Series. [accessed 2019 June 05].

https://apps.who.int/iris/bitstream/handle/10665/42665/WHO_TRS_916.pdf;jsessionid=387936955093F88C3F42370BEA1219D2?sequence=1.

Vissers M, Das AB (2018) Potential mechanisms of action for vitamin C in cancer: reviewing the evidence. *Front physiol*; 9: 809. <https://doi.org/10.3389/fphys.2018.00809>

Chen Q (2012) Vitamin C in cancer treatment: Where pharmacokinetics speaks. *J Drug Metab Toxicol*; 3: e107. <https://doi.org/10.4172/2157-7609.1000e107>

Takahashi H, Mizuno H, Yanagisawa A (2012) High-dose intravenous vitamin C improves quality of life in cancer patients. *Pers Med Universe*; 1: 49-53.

<https://doi.org/10.1016/j.pmu.2012.05.008>

Carr AC, Rosengrave PC, Bayer S, et al (2017) Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. *Crit Care*; 21: 1-10.

<https://doi.org/10.1186/s13054-017-1891-y>

Lykkesfeldt J, Tveden-Nyborg P (2019) The pharmacokinetics of vitamin C. *Nutrients*; 11: 2412. <https://doi.org/10.3390/nu11102412>

Marik PE, Khangoora V, Rivera R, et al (2017). Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*; 151: 1229-1238. <https://doi.org/10.1016/j.chest.2016.11.036>

Hill A, Clasen KC, Wendt S, et al (2019) Effects of vitamin C on organ function in cardiac surgery patients: A systematic review and meta-analysis. *Nutrients*; 11: 2103. <https://doi.org/10.3390/nu11092103>

Fukushima R, Yamazaki E (2010) Vitamin C requirement in surgical patients. *Curr Opin Clin Nutr Metab Care*; 13: 669-676. <http://doi.org/10.1097/MCO.0b013e32833e05bc>

- Blass SC, Goost H, Tolba RH, et al (2012) Time to wound closure in trauma patients with disorders in wound healing is shortened by supplements containing antioxidant micronutrients and glutamine: a PRCT. *Clin Nutr*; 31: 469-475. <https://doi.org/10.1016/j.clnu.2012.01.002>
- Cereda E, Gini A, Pedrolli C, et al (2009) Disease-specific, versus standard, nutritional support for the treatment of pressure ulcers in institutionalized older adults: a randomized controlled trial. *J Am Geriatr Soc*; 57: 1395-1402. <https://doi.org/10.1111/j.1532-5415.2009.02351.x>
- De Francesco EM, Bonuccelli G, Maggiolini M, et al (2017) Vitamin C and Doxycycline: A synthetic lethal combination therapy targeting metabolic flexibility in cancer stem cells (CSCs). *Oncotarget*; 8: 67269. <https://doi:10.18632/oncotarget.18428>
- Kaźmierczak-Barańska J, Boguszewska K, Adamus-Grabicka A, et al (2020) Two faces of vitamin c- Antioxidative and pro-oxidative agent. *Nutrients*; 12: 1501. <https://doi.org/10.3390/nu12051501>
- Mehdad S, Mansour S, Aguenou H, et al (2020) Diet, weight status, and physical activity in cancer prevention. *NAJFNR*; 4: 325-335. <http://dx.doi.org/10.5281/zenodo.4299554>
- Mentella MC, Scaldaferrri F, Ricci C, et al (2019) Cancer and Mediterranean diet: a review. *Nutrients*; 11: 2059. <https://doi.org/10.3390/nu11092059>