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European Association for the Study of Obesity (EASO) Position Statement on medical nutrition therapy for the management of individuals with overweight or obesity and cancer

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Short Title: Medical nutrition therapy and cancer

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Abstract

Obesity, a prevalent and multifactorial disease, is linked to a range of metabolic abnormalities, including insulin resistance, dyslipidemia, and chronic inflammation. These imbalances not only contribute to cardiometabolic diseases but also play a significant role in cancer pathogenesis. The rising prevalence of obesity underscores the need to investigate dietary strategies for effective weight management for individuals with overweight or obesity and cancer. This European Society for the Study of Obesity (EASO) position statement aimed to summarize current evidence on the role of obesity in cancer and to provide insights on the major nutritional interventions, including the Mediterranean diet (MedDiet), the ketogenic diet (KD), and the intermittent fasting (IF), that should be adopted to manage individuals with overweight or obesity and cancer. The MedDiet, characterized by high consumption of plant-based foods and moderate intake of olive oil, fish, and nuts, has been associated with a reduced cancer risk. The KD and the IF are emerging dietary interventions with potential benefits for weight loss and metabolic health. KD, by inducing ketosis, and IF, through periodic fasting cycles, may offer anticancer effects by modifying tumor metabolism and improving insulin sensitivity. Despite the promising results, current evidence on these dietary approaches in cancer management in individuals with overweight or obesity is limited and inconsistent, with challenges including variability in adherence and the need for personalized dietary plans.

1. Introduction

Obesity, a chronic and multifactorial disease, has reached epidemic proportions globally, significantly impacting public health. Its association with various metabolic abnormalities, including insulin resistance, dyslipidemia, and chronic inflammation, is well documented [1]. These metabolic imbalances are not only linked to the development of cardiovascular diseases and type 2 diabetes but also play a critical role in the pathogenesis of several types of cancer [2, 3]. With rising obesity rates, there is an urgent need to explore effective dietary strategies for weight management in individuals with cancer and cancer prevention in individuals with overweight or obesity.

Given the complex relationship between diet, obesity, and cancer, there is a growing interest in understanding how nutritional interventions can be integrated into cancer prevention and treatment strategies [4]. Numerous clinical trials are currently underway to assess the effectiveness of different nutritional interventions in cancer patients, particularly those with obesity-related cancer.

Adopting a balanced diet rich in plant-based foods has been associated with a reduced risk of developing various types of cancer [5]. The Mediterranean Diet (MedDiet), in particular, characterized by a high intake of fruits, vegetables, legumes, whole grains, and moderate consumption of extra virgin olive oil, fish, and nuts, has been correlated with a decreased risk of several cancers [6]. This dietary model not only promotes a healthy body weight but also provides nutrients and bioactive compounds that may have synergistic protective effects against cancer development [6].

Among other dietary interventions, the ketogenic diet (KD) has recently garnered significant attention. Initially developed to manage drug-resistant epilepsy in children, KD has shown potential benefits in promoting weight loss and improving metabolic profiles in individuals with obesity [7]. By drastically reducing carbohydrate intake, KD induces a state of ketosis, where ketone bodies become the primary energy source, potentially exerting anticancer effects by altering tumor metabolism and reducing insulin levels [8].

Intermittent fasting (IF) is another dietary approach that has gained popularity for obesity management [9]. IF involves periodic cycles of fasting and eating, which can improve insulin sensitivity, reduce inflammation, and promote weight loss [9]. Variants of IF have shown promise in improving metabolic health and a potential role in in the prevention and treatment of cancer [10].

However, current evidence on the role of dietary interventions like KD and IF in cancer management is limited and inconsistent. Challenges include the lack of standardized nutritional guidelines, variability in dietary adherence, and the need for personalized dietary plans based on individual metabolic and genetic profiles. Therefore, well-designed clinical trials and comprehensive nutritional assessments are essential to establish the efficacy and safety of these dietary interventions in cancer care.

This position statement of the European Society for the Study of Obesity (EASO) aimed to provide an overview of the current evidence on the role of obesity in cancer and the major nutritional interventions in the treatment of obesity-related cancers, highlighting ongoing clinical trials and potential mechanisms through which these diets may influence management and prognosis. Then, it aimed to provide clinical insights that should be adopted in the medical nutritional management of individuals with overweight or obesity and cancer.

2. Obesity and cancer

Several epidemiological studies have shown an association between obesity and cancer, in terms of increased incidence, risk of progression and relapse [11-13]. Experimental and clinical data provided possible cause-effect relationship, but further studies are needed to prove a causality process linking obesity and cancer [14]. Continuous Update Project (CUP) database of the American Institute for Cancer Research (AICR) is an ongoing program that analyzes global research on how diet, nutrition and physical activity affect cancer risk and survival and provides a continuous update of 17 different types of cancer: endometrial, ovarian cancer, esophageal, stomach, postmenopausal breast cancer, liver, colorectal, kidney, gallbladder, pancreatic, prostate, bladder, skin, lung, mouth, pharynx and larynx cancer [15]. Among these types of tumors, in the present study, we will consider the main obesity-related cancers: endometrial, ovarian, esophageal, stomach, postmenopausal breast cancer, liver, colorectal, kidney, gallbladder, pancreatic and prostate.

2.1. Obesity and cancer: epidemiology and relative risk

Breast cancer is the most common cancer in women worldwide and is associated with a greater risk of developing in postmenopausal women with obesity, especially for BMI >35.0 kg/m2 [16]. The relative risk (RR) was 1.40 (CI 1.31-1.49) with a 10 kg/m2 increase in BMI [17] or 1.12 [95% confidence intervals (CI) 1.08-1.16] with a 5 kg/m2 increase in BMI [12]. It is worthy to note that obesity, both before and after 30 years of age, decreases the risk of premenopausal breast cancer and especially the risk of all estrogen receptor (ER)/ progesterone receptor (PR)/ human epidermal growth factor receptor 2 (HER2)-defined subtypes of breast cancer [18, 19]. In this context, obesity is inversely associated with PR and ER-positive premenopausal breast cancer [20]. In contrast, obesity is a risk factor for postmenopausal hormone receptor-positive breast cancer [16, 21]. Among women, endometrial cancer is more strongly associated with obesity than any other cancer type [22]. The RR was 2.89 (95%CI 2.62-3.18) with a 10 kg/m2 increase in BMI [17] or 1.59 (95%CI 1.50-1.68) with a 5 kg/m2 increase in BMI [12]. Compared with women with a normal weight, the RR of mortality for women with moderate obesity (BMI 35-39.99 kg/m2) is 2.53, and for severe obesity (≥ 40 kg/m2) is 6.25 [11]. Moreover, obesity is also associated with a worse outcome [23]. Patients with obesity show more complications related to surgery, radiation, and chemotherapy and both systemic chemotherapy and endocrine therapy are less effective [24]. Although the association is not as strong as with endometrial cancer, obesity is also related to the risk of developing ovarian cancer [25]. The RR was 1.14 (95%CI 1.03-1.27) with a 10 kg/m2 increase in BMI or 1.03 (95%CI 0.99-1.08) with a 5 kg/m2 increase in BMI [12]. The visceral fat seems more linked to the development of ovarian cancer than BMI per se [26]. There are several risk factors for esophageal adenocarcinoma (EAC) and gastroesophageal junction cancer. The RR for EAC occurrence is 1.52 (95%CI 1.33-1.74) for each 5 kg/m2 increase in BMI in men and 1.51 in females [12]. Obesity is not linked to EAC only due to an anatomic matter, since abdominal obesity is associated with Barrett's esophagus even after adjusting for the presence of reflux. A multicenter study demonstrated an association of visceral adiposity, measured by computed tomography, with esophageal and junctional adenocarcinomas [27]. In Western countries, a large amount of hepatocellular carcinoma (HCC) developed from metabolic dysfunction-associated steatotic liver disease (MASLD), which is in turn closely associated with obesity and type 2 diabetes mellitus [28]. Therefore, obesity was related to increased cirrhosis, HCC and risk of death, particularly for male patients with moderate obesity (RR 4.52 (95%CI 2.94–6.94)) [11]. Over 40% of kidney (renal cell) cancer (RCC) seems to be associated with obesity assessed based on BMI. The RR was 1.24 (95%CI 1.15-1.34) for men and 1.34 (95%CI 1.25-1.43) for women with a 5 kg/m2 increase in BMI [12]. The RR of the highest BMI

category versus normal BMI was 1.8 (95%CI 1.7-1.9), according to a strong body of evidence [13]. A large, prospective study revealed that weight gain until 50 years of age strongly correlated with the incidence of RCC [29]. The Metabolic Syndrome and Cancer Project (Me-Can) showed that increased levels of BMI, blood pressure, glucose and triglycerides were associated with increased risk of RCC among men, while high BMI was most important in women [30]. The relationship between obesity and colorectal cancer (CRC) development has been evaluated in several epidemiological studies [11-13]. The RR was 1.24 (95%CI 1.20-1.28) for men and 1.09 (95%CI 1.05-1.13) for women with a 5 kg/m2 increase in BMI and the association was stronger in men than in women [12, 31]. The RR for CRC was higher in patients with obesity in comparison to patients with BMI < 25 kg/m2 [32]. In a large meta-analysis, higher BMI was significantly associated with more favorable CRC outcomes, even though higher BMI/obesity is an established determinant for the development of CRC [33]. The impact of obesity on the incidence of gallbladder cancer is more pronounced in women [men 11%, RR 1.09 (95%CI 0.99–1.21), women 42%, RR 1.59 (95%CI 1.02–2.47)] and the RR of death from gallbladder cancer for a BMI 30.0-34.99 kg/m2 was 2.13 for women and 1.76 for men [11]. Beyond molecular mechanisms, obesity may act indirectly by increasing the risk of gallstones [34]. The RR for pancreatic cancer occurrence was 1.16 (95%CI 1.05-1.28) for each 5 kg/m2 increase in BMI in men and 1.10 (95%CI 1.02-1.09) in women [35] with an increased mortality in female with BMI >40 kg/m2 (female RR 2.76 (1.74–4.36)). The relationship between BMI and prostate cancer has also been much discussed [12, 36]. Cancer-related mortality for male patients with moderate obesity showed a RR of 1.34 (95%CI 0.98–1.83) [11]. While a high BMI was positively related with non-metastatic high-grade prostate cancer, it was inversely related with the risk of low-grade tumour [37].

In summary, obesity significantly increases the risk for various cancers, especially in postmenopausal women. It is strongly associated with breast, endometrial, colorectal, and kidney cancers, among others. The presence of visceral fat plays a critical role in cancer development, particularly in ovarian and esophageal cancers. Additionally, obesity influences cancer prognosis, often leading to poorer outcomes and complicating treatment efficacy. The relationship between obesity and cancer is complex, with some cancers showing differing risk profiles depending on factors like fat distribution and tumor type

2.2. Obesity and cancer: mechanisms

The underlying mechanisms explaining the association between obesity and cancer consider adipose tissue and adiponiche (i.e., adipose tissue stem niche) as the main driver. During the expansion of adipose tissue, the adiponiche become dysfunctional, contributing to the development of obesity and metabolic complications [38-41]. Hypoxia occurs when the rapid expansion of adipose tissue has not been supported by an adequate capillary network [42]. Hypoxia induces pro-angiogenic factors, such as vascular endothelial growth factor and hypoxia-inducible factor 1α (HIF-1α), that have been implicated in breast cancer biology [43]. Moreover, hypoxia stimulates adipose tissue to produce other proinflammatory cytokines, such as tumour necrosis factor α (TNF-α), that enhance fibrosis, a process involved in carcinogenesis. The dysfunctional adipose tissue induces also a dysfunctional immune system with increased pro-inflammatory M1-polarised adipose tissue macrophages, reduced levels of regulatory T cells (Tregs), of eosinophils and their anti-inflammatory interleukine (IL)-4 and IL-13, and of M2-polarised anti-inflammatory adipose tissue macrophages [41]. Furthermore, the inflammasomes, activated by fatty acids and high glucose levels, induce inflammatory IL-1β and IL-18, promoting inflammatory microenvironment surrounding cancer cells, in particular in CRC [44, 45]. Adipose stromal/stem cells (ASCs) are influenced by microenvironment and cell-to-cell

interactions to support physiological adipose tissue expansion [41, 42]. An increase of ASCs, present in obesity, was also describe on CRC and seems to sustain tumour growth [46]. Adipocytes are the most important cells of the adipose tissue implicated in the modulation of the microenvironment and thus of the tumour growth through paracrine, autocrine and endocrine ways. Adipocyte-derived factors include adipokines, extracellular matrix (ECM) components, hormonal factors, growth factors and inflammatory cytokines [47]. In mice, loss of adiponectin enhances development of colitis-associated CRC [48], while adiponectin released from perinephric adipose tissue may impact RCC aggressiveness [30]. On the other hand, leptin induces TNF-α and IL-6 and, in an in vitro study, stimulated lipid droplets increasing cell proliferation [49]. The insulin growth factor (IGF) pathway, whose is upregulated in obesity, demonstrated a crucial role in the development of EAC. Studies have also found associations between leptin/adiponectin and Barrett's esophagus presence and progression to EAC. Moreover, peritumoral adipose tissue in patients affected by EAC showed increased adipocyte size and inflammation markers, high levels of leptin, increased angiogenesis and was associated with lymph node invasion. The leptin receptor G2548A mutation is statistically significantly associated with an increased risk of prostate cancer. Moreover, patients with high-volume prostate cancer had higher serum leptin levels [37]. The chronic low-grade inflammation characterizes not only the visceral and subcutaneous adipose tissue but also the breast fat and it is associated with activation of signaling pathways, including LKB1/AMPK, p53, HIF1α and PKM2. This produces the increased levels of aromatase, whose usually limit estrogen biosynthesis, causing production of estrogens, particularly estradiol, determining breast cancer growth and progression [50-53]. Interestingly, it was found an involvement in creatine synthesis by peritumoral adipocytes in the development of breast cancers in obese mice [54]. Creatine is implicated in T cell development and macrophage polarization [55] and is transported into the cancer cells, producing cell growth and larger tumors, possibly due to an increased cell energy supply [54]. This is consistent with the observation that mitochondrial creatine kinase is stabilized in HER2+ breast cancer, increasing cytosolic phosphocreatine and thus cytosolic energy supply [56]. It was recently demonstrated that Casein Kinase 2 (CK2) covers a pivotal role in obesity, stimulating adipocyte hypertrophy/hyperplasia and adipogenesis resulting in the adipose tissue expansion [57]. CK2, usually overexpressed in cancer, contribute to the regulation of aberrant lipid metabolism in malignant cells, leading to upregulation of protein-kinase B (AKT), Wnt and extracellular signal-regulated kinase (ERK) and to downregulation of tumour suppressor molecules [58, 59]. The involvement of microbiota dysregulation in obesity and related diseases, such as cancer it was described [38]. Short-chain fatty acids (SCFAs) produced by bacteria are decreased in obesity, with a reduction in triglyceride hydrolysis, free fatty acids (FFA) oxidation, beige adipogenesis and mitochondrial biogenesis [60, 61]. Indeed, microbiome-derived peptides modulate immune cell activity and leakage of lipopolysaccharides (LPS) activates Toll-like receptor 4 (TLR4) and nuclear factor-kB (NF-kB), leading to inflammatory-induced carcinogenesis in the CRC and HCC [62, 63].

In summary, the adipose organ and cancer crosstalk, through out several mechanisms, that adipose organ and tumor share, determine the role of obesity in cancer development, progression, invasiveness and chemoresistance.

3. Role of nutrition in obesity and cancer risk

Excess adipose tissue is known to be an independent risk factor for cancer. Adopting a healthier lifestyle can lead to a lower body weight, however overall healthy dietary pattern may also contribute to cancer prevention.

A healthy dietary pattern includes a high intake of vegetables, pulses, berries, fruits, whole grains, nuts, seafood and fish, low-fat dairy, and a low intake of red meat and processed meat [64]. Furthermore, a healthy dietary pattern is low in sugary foods and beverages, as well as in ultra-processed starch and fats. The energy intake in balance with energy expenditure, is one of the components in a healthy diet. A diet rich in various bioactive compounds, such as in the MedDiet may have a favorable impact on obesity and cancer risk. The best healthy dietary strategy can be sustained over a long period, leading to improved health and weight outcomes for people living with obesity [65]. Registered dietitians can provide medical nutrition therapy to support people in adopting individualized, realistic, and sustainable healthy eating patterns as a part of multidisciplinary obesity care plan [66]. It should be recognized that the modern food environment with unlimited access to highly palatable, energy dense foods often challenge dietary patterns and weight management.

Fruits, vegetables, and pulses are crucial components of a healthy diet and recommended by the World Health Organization (WHO) [67] and the World Cancer Research Fund (WCRF) for cancer prevention [68]. Intake of more than 400g per day of fruits, berries and non-starchy vegetables have health benefits and may reduce the cancer risk. Fruits and vegetables are rich in dietary fiber, as well as in a variety of vitamins, minerals, antioxidants, and bioactive compounds. Antioxidants and phytochemicals such as alkaloids, flavonoids, polyphenols, vitamin C and E may have potential benefits in cancer prevention in reducing inflammation and acting as an anti-carcinogen in scavenging free radicals [69]. It is recommended that people should consume a diverse range of colorful vegetables, fruits, and berries to maximize their nutrient intake because the content of these nutrients can vary significantly. Pulses, such as beans and lentils, are also essential sources of dietary fiber, proteins, and other nutrients. Many vegetables have a high content of water and dietary fiber, contributing to the volume and low energy density in a meal and may facilitate weight management, thereby reduce the risk of cancer.

Foods rich in whole grains are also important for cancer prevention, especially for reducing the risk of colorectal cancer. Examples of whole-grain-rich foods include unprocessed maize, oats, rye, barley, millet, and wheat. When whole grains are processed, the nutrient-dense bran and germ are removed, which reduces the amount of fiber and other beneficial nutrients.

Furthermore, a high intake of dietary fiber (25-29 g) in people with or without chronic disease has been associated with a lower body weight and lower risk of colorectal cancer, breast cancer, a total cancer, and cancer mortality in a large systematic review and meta-analysis [70]. The dose-response findings were similar for dietary fiber as well as for whole grains and the risk reduction of cancer. The high fiber content in whole grains, fruits, and vegetables promotes a feeling of fullness and satiety, and may therefore facilitate weight management which is beneficial in cancer prevention. The recommended total daily fiber intake is at least 30 g, according to the WCRF [68].

High consumption of red and processed meat may increase the risk of colorectal cancer [68]. Red meat includes e.g., pork, beef, and lamb, whereas white meat includes poultry, such as chicken and turkey. Processed meat is preserved by smoking, salting, curing, or adding chemical preservatives, such as bacon and sausages. For cancer prevention, it is recommended to limit the consumption of processed meat as much as possible, and the intake of red meat should be maximum 350-500 grams per week in cooked weight [68]. However, meat also provides valuable nutrients such as iron, zinc, vitamin B12 and protein, and can be part of a healthy diet. It is

particularly important to consider when providing medical nutrition therapy after metabolic and bariatric surgery.

Alcohol consumption increases the risk of various types of cancer, including breast cancer, mouth and pharynx and larynx cancers, colorectal cancer, stomach cancer, liver cancer, kidney cancer and esophageal cancer according to the WCRF [68]. There is no established minimum safe level of alcohol consumption, and it is recommended that alcohol intake be kept to a minimum to reduce the risk of cancer. Alcohol has a high energy content (7 kcal/g) and can therefore contribute to increased energy intake and challenges in weight management [68].

There are recommendations that people should not use dietary supplements for cancer prevention [68]. However, people living with obesity may sometimes require dietary supplementation with vitamins and minerals such as vitamin D, vitamin B12, Calcium and iron to meet their nutritional needs. This is the case for example after metabolic and bariatric surgery since the intake and absorption of these nutrients may be reduced [68].

The intake of sugar-sweetened drinks should be restricted because these beverages can contribute to challenges in weight management [68]. Increased body weight is associated with cancer. Drinking an adequate amount of water helps to maintain a sufficient level of hydration and is the optimal beverage choice. The shift from sugar-sweetened drinks to beverages with artificial sweeteners may help reduce energy intake in people who consume sugar-sweetened beverages. A systematic review and meta-analysis of 17 randomized controlled trials reported that changing sugar-sweetened drinks to artificial sweetened beverages may contribute to small improvement in weight status [71]. Nevertheless, the WHO has recently recommended that artificial sweeteners should not be used to control body weight owing to the limited evidence, primarily from observational studies [72]. Instead, the focus should be on enhancing overall healthy eating patterns and decreasing free sugar intake. The artificial sweetener aspartame was recently classified as “possible carcinogenic to humans” (Group 2B) by the International Agency for Research on Cancer (IARC) [73]. The classification was based on limited evidence, and Group 2B is the lowest evidence category for carcinogens. The WHO has not changed the acceptable daily intake (ADI) of aspartame (40 mg/kg body weight/day) based on the new classification. The European Food Safety Authority (EFSA) evaluation of aspartame safety and ADI recommendations aligns with the conclusion of the WHO [74].

4. Nutritional approaches in individuals with obesity and cancer

4.1. Mediterranean diet

Historically, the MedDiet has been initially proposed as a healthy pattern diet [75] that combines certain foods and nutrients which interact synergically between each other, and has been revealed to be associated with a reduction in the risk of cardiovascular diseases and overall mortality [76]. Subsequently several epidemiological studies have shown a strong correlation between a higher adherence to the MedDiet and a lower incidence (i.e., new onset and prevention) of several forms of cancers (colorectal, breast, stomach, pancreas, prostate, and lung cancer) [77-79]. On the other hand, the period during cancer (the active phase), or in other words, immediately after diagnosis and during treatment, remains critical and crucial [80], since important health-related outcomes occur due to the nature of the cancer by itself or as an adverse consequence of treatment (e.g., chemotherapy, radiotherapy etc.) [80]. Most commonly, weight loss and cachexia occur in the course of cancer treatment, however with the aim of preventing/treating malnutrition in this population, strong nutritional evidence for adults with cancer is available and guidelines have been established [81]. Interestingly, in certain

cancers and/or treatments, different kinds of changes are observed such as weight gain [82], increased body fat mass and its central visceral deposition [83], as well as a reduction in muscle mass and strength, leading to sarcopenic obesity in this population (that is, with cancer and obesity). This unavoidably increases the development of cardiometabolic risk factors (metabolic syndrome/obesity, hyperglycemia/diabetes, dyslipidemia, and hypertension) [84, 85], as well therapy-induced inflammation [86]. In this scenario, the treatment of patients with cancer becomes extremely challenging [87], especially as excess body weight (i.e., obesity) represents one of the main factors for a poorer prognostic outcome for certain cancers (chemotherapy resistance, rate of remission and recurrence, survivorship and mortality, etc.) [87]. In this case, evidence for dietary interventions during cancer treatment is very limited [88], as no clear nutritional indications are available in this population (cancer and obesity). Additionally, during this particular period, namely immediately after diagnosis, as well as during cancer treatment, in the past few years, emerging data have proposed the MedDiet to have the potential to improve the clinical and supportive-care outcomes in adults with cancer [89]. However, the evidence available regarding the effects of the MedDiet in patients with active cancer has not been extensively evaluated, especially in people with obesity [90].

With this aim in mind, some recent randomized controlled trials have been conducted on people with cancer and obesity (mean BMI≈30 kg/m2) [91-97]. In general according to the available data, it can be summarized, as the MedDiet in these studies was delivered over a mean period of six months, and it appeared to be safe and feasible in people with cancer (breast, lung and prostate) while co-existing with obesity, due to no/very few adverse events, as well as high adherence and low attrition (i.e., dropout) rates [91-97]. Moreover, the dietary composition and patterns used in these studies were mainly calorie-restricted [91, 94], rich in fibres (wholegrain, legumes, fruit, and vegetables) [91, 95, 98], and monounsaturated fatty acids (olive oil), as well as low in saturated fatty acids [91, 95, 97, 98], and were revealed to have beneficial effects in terms of heath indicators such as anthropometric variables [body weight, waist circumference (WC)] [91-93, 95-97], body composition (fat and lean mass) [91, 95, 97] and biomarker indicators (inflammation, glycemic and lipid profiles) [91-93, 95, 96, 98, 99], as well as other cancer outcomes (i.e., quality of life) [91, 93-96, 99].

For instance, the MedDiet approach in people with cancer (mainly breast but also prostate cancer) and obesity appears to be associated with a significant reduction in body weight [91, 95-97], WC [95, 97] and total body fat [91, 95, 97] but, in some cases, it may lead to a reduction in lean mass (LM) [91, 100], when compared with patients who were in “usual care” during which they were not on a clear dietary intervention, resulting in being more prone to regaining weight with significantly increased BMI [97] and WC [92] or, in the best scenario, no changes were detected in the anthropometric variables and body composition compartments in these arms (i.e., no increase) [95]. Moreover, in patients with breast, lung and prostate cancer, the MedDiet was found to be associated with improvements in certain biomarkers such as those related to lipid and glycemic profiles, as well as inflammation. Thus, the MedDiet has been related to a reduction in blood triglycerides [96], glycemia [97, 98] and IL-8 [91], and the advanced lung cancer inflammation index (ALI) [98], as well as an increase in high density lipoprotein (HDL) cholesterol levels [95-97]. On the other hand, the “usual care” arms reported no ameliorative changes in these biomarkers, or in some studies led to a deterioration of some of these parameters, such as an increase of total cholesterol and low density lipoprotein (LDL) cholesterol [101]. Moreover the MedDiet appeared to improve patients’ general condition in terms of global health and quality of life [95], reduction of stress [94] and cancer-related fatigue [93], even in the absence of significant changes in body weight status (i.e., reduction). Last but not least, very recent data deriving from a small cohort study (i.e. not randomized controlled

trial) of patients with advanced melanoma, revealed that higher adherence to the MedDiet was associated with a higher probability of response to treatment with immune checkpoint blockade (ICB) [102]. ICB is a relatively new and highly successful treatment against severe cancers used in immunotherapy to enhance the immune system [103].

The mechanisms behind the beneficial impact of MedDiet on both cancer (i.e., during the active phase) and obesity outcomes are complex and still not fully understood [104]. However, we speculate that some nutrients, specifically polyphenols (e.g., olive oil, red wine, nuts and seeds), fibres (e.g., whole grains, fruits and vegetables), and omega-3 fatty acids (e.g., fish), that are a significant part of the MedDiet, may explain and could be behind these benefits.

For example several preclinical investigations showed the positive effect of polyphenols (i.e., curcumin) in limiting weight gain [105] and the decrease of fat storage [106], and for these two properties, it has been proposed as an anti-obesity strategy, however clinical studies are still limited [107]. In terms of cancer, the dietary polyphenols (flavonoids, phenolic acids) are known to prevent cancer (i.e., lung, gastric, colorectal, breast and prostate), through antioxidant and anti-inflammatory mechanisms, as well as the modulation of multiple molecular events involved in carcinogenesis [108]. In addition to that, some early clinical investigations found that natural polyphenols can be considered as potential candidates for anticancer therapy, by acting on premalignant forms (i.e., familial adenomatous polyposis [curcumin and quercetin]) [109], or as a coadjutant to traditional cancer treatments [110, 111], for example, by enhancing the efficacy of radiotherapy in breast cancer, overcoming chemotherapy resistance in pancreas cancer (epigallocatechin gallate [curcumin]) or reducing the recurrence rate (colon rectal cancer [flavonoid]) [112].

Secondly, the MedDiet is characterized by a high intake of fibers which seems to act on the intestinal microbiota, modulating its “composition” and “activity” in terms of production of metabolites regulating the immune function and inflammatory pathways [113]. In particular, a high fiber diet such as the MedDiet, seems to increase the number of intestinal bacterial species responsible for the production of SCFAs (acetate, propionate, and butyrate) [114, 115], important for the proper functioning of the immune system and the prevention of inflammatory diseases [115]. Recently, the same SCFAs were proposed to have a protective effect against obesity by increasing appetite control and satiety, as well as energy expenditure - however, such a relationship needs further confirmation [116, 117]. In terms of cancer, SCFAs seem to induce cell apoptosis and suppress cell proliferation and metastasis in several types of cancers (lung, breast, bladder, gastric cancer), but mainly colorectal cancer [118]. Moreover, they reduce anticancer drug resistance, such as that associated with anticancer drug chemotherapy [118].

Finally, the MedDiet ensures a high intake of omega-3 polyunsaturated fatty acids (PUFAs). While the anti-inflammatory and triglyceride-reducing properties of long-chain PUFAs are well established [119], the anti-obesity effect in humans remains under debate, since published research suggests that even if omega-3 PUFAs may be not helpful in losing body weight, they are able to limit weight regain in the longer term, and for this reason they can be useful during the weight-loss maintenance phase [120]. In terms of cancer, epidemiological studies link high dietary PUFAs intake with a reduced incidence of cancer (colorectal, breast) [121, 122]. Moreover, in breast cancer, the role of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation as an adjunctive measure has been explored in reducing chemotherapy-associated weight gain and muscle loss (sarcopenic obesity) [122, 123]. In the same direction, dietary PUFAs may improve the efficacy and tolerability of cancer chemotherapy drugs (in colorectal cancer) [121]. Finally, higher intakes of EPA and DHA from dietary sources were

reported to be associated with a reduction in breast cancer recurrence and improved overall mortality in early stage breast cancer [123, 124].

Recommendations

The MedDiet is ideal for almost all cancer patients, particularly during treatment phases, as it helps manage weight, cachexia, and improves quality of life (Fig.1). It is also beneficial for those at high risk of metabolic complications, including metabolic syndrome, dyslipidemia, and hypertension. However, it should be avoided by those with severe allergies to key MedDiet components (such as nuts) and adjusted for patients undergoing specific cancer treatments based on their guidelines. Individuals with gastrointestinal issues affecting nutrient absorption may need a modified version of the diet. The MedDiet should consist of 45-55% of daily calories from complex carbohydrates (whole grains, legumes, fruits, vegetables), 15-25% from lean proteins (fish, poultry, legumes, nuts), and 25-35% from healthy fats (olive oil, nuts), with a focus on limiting saturated fats. Aim for a daily fiber intake of 25-35 grams from high-fiber foods to support overall health and manage both obesity and cancer outcomes.

4.2. Ketogenic diet

KD is a dietary pattern characterized by high fat intake, moderate-to-low protein consumption, and very-low-carbohydrate intake (<50 g) [8]. Initially, the KD was employed to treat drug-resistant epilepsy in children, but it has now gained widespread acceptance for obesity management. Due to the connection between obesity, diet, and cancer, there is a growing interest in using the KD as an adjuvant therapy in cancer treatment [125, 126]. Preclinical and some clinical trials have shown that the KD can be cost-effective and relatively well-tolerated, with the potential to improve metabolic abnormalities, reduce inflammation, limit tumor growth, and protect healthy cells from the damage caused by chemotherapy and radiation [126].

With a diet that limits intake of carbohydrate, glucose availability for glycolysis is limited, preventing the formation of pyruvate and subsequent conversion to lactate to generate ATP [127]. Lipid and ketone bodies become the predominant source of energy and require the cell to use mitochondria, which may be dysfunctional in cancer cells as noted above. This combined with limited availability of glucose for the pentose phosphate pathway and generation of NADPH, leads to oxidative stress in cancer cells compared with normal cells [127]. Evidence of this oxidative stress was demonstrated in mouse models of neuroblastoma through measurement of activation of energy sensor adenosine monophosphate (AMP)-activated protein kinase (AMPK) [128]. In response to KD, they found higher activation of AMPK in tumor tissue but not in normal tissue [128]. It is important to note that a few mitochondrial enzymes are key in metabolism of ketone bodies for energy, and tumor cells tend to express these enzymes in varying amounts. Zhang et al demonstrated that expression of genes encoding the two ketolytic enzymes 3-hydroxybutyrate dehydrogenase 1 (BDH1) and succinyl-CoA:3-oxoacid CoA transferase 1 (OXCT1) in tumor cells correlated with response to KD [129].

In addition to these metabolic benefits, KD perhaps through action of ketone bodies, can exert several other benefits, including modulation of signaling molecules, gene expression, as well as reduction in inflammation [126]. β-hydroxybutyrate and acetone have been noted to modulate the signaling of N-methyl-D-aspartate (NMDA), which is physiologically relevant as NMDA receptor expression has been observed in various types of cancers [130]. Similarly, hydroxy-carboxylic acid receptor 2 (HCA2) is activated by β-hydroxybutyrate [131]. HCA2 is described as a tumor suppressor and activates specific macrophages that have neuroprotective effects [131]. KD and ketone bodies have also been associated with anti-inflammatory effects through

reduction in cytokines such as TNF-α, IL-1, and IL-6 [126]. A recent study in a mouse model of colon cancer noted that a KD was associated with lower tumor weight, as well as plasma IL-6 levels [132]. Additionally, blood ketone body concentrations were also negatively correlated with tumor weight [132]. KD also reduces inflammation through suppression of NLRP3 inflammasome, which is a multiprotein complex that controls the activation of capase-1 and subsequent release of proinflammatory cytokines [133]. β-hydroxybutyrate was shown to inhibit assembly of NLRP3 inflammasome [133].

Despite these theoretical benefits, clinical trials with KD are quite limited [134]. A recent review of clinical trials regarding use of KD in cancer noted that of the approximately 30 trials, the vast majority were case reports or pilot/feasibility studies, with most focusing on tolerability of KD in this population, as well as impact on body weight, glucose, and other metabolic parameters [126]. As an example, a clinical trial retrospectively evaluated 53 patients undergoing treatment for high-grade glioma who had adequate glucose values recorded [135]. Six of the 53 patients were on KD during treatment with micronutrient composition of 77% fat, 8% carbohydrate, and 15% protein. They noted that the mean blood glucose for patients on a standard diet was 122 mg/dl, whereas that of patients on a KD was 84 mg/dl and decreased from 142.5 mg/dl prior to initiation of KD [135]. Another clinical trial randomized 73 women with ovarian or endometrial cancer to either a KD (energy from fat, protein, and carbohydrate of 70:25:5) or a diet recommended by the American Cancer Society [136]. After 12 weeks, KD resulted in lower overall and central fat mass. There was also a 21.2% reduction in visceral fat mass with KD compared with 4.6% with the American Cancer Society diet along with a more significant reduction in insulin, C-peptide levels, glucose, and IGF-1 levels [136]. KD also showed more significant improvement in physical function scores, reports of fatigue, as well as cravings for starchy foods and fast-food fat [137].

Another randomized clinical trial was designed to enroll three cohorts including patients with breast, rectal, and head and neck cancer and included two interventions: ketogenic breakfast with a ketogenic drink and whole-food KD [138]. However, ketogenic breakfast drink was not tolerated by many, thus limiting the data to individuals with nonmetastatic breast cancer comparing either whole-food KD (n = 29) or standard diet (n = 30). Authors noted that the KD was well-tolerated and resulted in body weight loss of 0.4 kg per week, as well as fat mass. Although fat-free mass and skeletal muscle mass declined initially, it was subsequently preserved. Insulin and IGF-1 levels also decreased more in the KD group [138].

The potential contraindications of KD in patients with cancer come from in vitro studies and some early-stage in vivo evidence [139, 140]. In a preclinical model of tuberous sclerosis complex, a rare genetic disorder, the growth of renal lesions in Eker rats (Tsc2+/-) was evaluated subjected to ad libitum prolonged feeding of KD for 4, 6, and 8 months [139]. The authors demonstrated that especially in its long-term usage, KD leads to excessive growth of renal tumors by recruiting ERK1/2 and mTOR, which is related to oleic acid accumulation and the overproduction of growth hormone. The authors also reported the exhaustion of the initial adaptive up-regulation of some protective proteins such as Nrf2, p53, and 8-oxoguanine glycosylase, suggesting that KD may be contraindicated in patients with tuberous sclerosis complex [139]. KD may also be contraindicated in cancer patients with the BRAF V600E mutation [140]. In a xenograft mouse model, the ketone body acetoacetate selectively enhanced BRAF V600E mutant-dependent MEK1 activation in human tumors, promoting the growth of human melanoma cells expressing this mutation [140].

Additionally, KD can be deficient in selenium, vitamin D, zinc, and other vitamins and minerals [8]. These potential adverse side effects can be prevented or corrected if KD is prescribed and monitored by a qualified nutritionist who selects appropriate patients, ensures KD is well-formulated and adjusted in food choices, and supplements with necessary vitamins and minerals [8].

In conclusion, data on the safety and efficacy of KD in cancer patients remain relatively sparse, and well-designed and rigorous clinical trials are urgently needed to evaluate the efficacy and safety of KD in the cancer setting.

Recommendations

The KD is suitable for patients with obesity and cancer who seek to manage weight and metabolic abnormalities while undergoing treatment (Fig.2). It may be beneficial for those needing to improve glucose regulation and reduce inflammation. However, KD may not be appropriate for patients with certain genetic mutations or conditions, such as tuberous sclerosis complex or BRAF V600E mutation, due to potential adverse effects. It may also result in deficiencies of essential nutrients, which can be managed with careful planning and supplementation by a qualified nutritionist. KD should consist of about 70-80% of daily calories from fat, 15-25% from protein, and 5-10% from carbohydrates. However, there are different ketogenic approaches, and the correct macronutrient composition may vary on a case-by-case basis. Regular monitoring and adjustment are necessary to ensure nutritional adequacy and safety.

4.3. Intermittent fasting

In recent decades, there has been a growing interest in IF as a strategy for managing obesity [141]. IF involves periodic episodes of minimal to no calorie consumption. The variations of IF include complete 24-hour fasting every other day or fasting on one or two non-consecutive days per week, commonly known as the 6:1 and 5:2 diets, respectively. Many IF programs recommend a minimal caloric intake (e.g., 500 kcal daily) during fasting periods, allowing unlimited consumption of calorie-free beverages. Another approach, time-restricted feeding (TRF), limits calorie intake to a specific window of time each day, typically between 4 and 12 hours. TRF may also involve calorie restriction during the non-fasting period, potentially offering additional benefits, such as improvements in circadian rhythm [141].

Emerging evidence suggests that fasting could play a key role in cancer treatment by fostering conditions that limit cancer cells' adaptability, survival, and growth [10]. Fasting could increase the efficacy of cancer treatments and limit adverse events. Yet, we lack an integrated mechanistic model for how these two complicated systems interact, limiting our ability to understand, prevent, and treat cancer using fasting [10].

Clinical studies have been carried out to measure the relevance of various modalities of IF on metabolic and hormonal endpoints correlated to cancer development and prognosis, given their practicality and the beneficial weight reduction effect in individuals with obesity [142]. IF has been demonstrated to improve cancer risk variables in several short-term randomized clinical studies, including lowered levels of glucose, insulin, leptin, and higher adiponectin, which are linked to cancer etiology [142]. TRF has been reported to cause substantial alterations in biochemical indicators linked to weight, including insulin sensitivity and oxidative stress in small and underpowered investigations [143, 144]. Nonetheless, in one study (n=116) in individuals with obesity on TRF, no significant change in weight, fasting insulin, or fasting glucose level was reported [145]. Furthermore, evidence shows that, unlike rats, people require weight loss to

optimize metabolic health [146]. Whether weight reduction has a causal function in lowering cancer risk and improving prognosis without considerable food composition changes remains a critical but unresolved issue [146].

A few studies have used IF in cancer patients as one of the regimens [147-150]. In one clinical trial of glioma with 25 patients, a significant decrease in HbA1c, insulin, and fat was observed, while lean body weight and ketone bodies (in the brain) were increased with a well-tolerated ketogenic IF diet [150]. Another study on 23 overweight premenopausal women with a high risk of breast cancer reported that 1 month of IF resulted in a 4.8% weight loss, 8% fat loss, and an improvement in insulin resistance [149]. Furthermore, a study that enrolled 13 stage II breast cancer women receiving (neo) adjuvant chemotherapy suggested that IF was well-tolerated, with a lower rate of withdrawals from adverse events [147]. In addition, fasting for a brief time was observed to minimize hematologic damage in women receiving chemotherapy, with the fasting group having considerably increased erythrocyte and thrombocyte levels following treatment. Following chemotherapeutic treatments, women in the control group exhibited higher DNA damage indicators and lowered circulating IGF-1 levels than those who had fasted and had lower IGF-1 levels [147]. In another clinical study of diverse tumor types, fasting for 24, 48, or 72 hours before treatment was determined to be possible and safe, with only minor adverse effects, such as weariness, headache, and dizziness [148]. Patients fasting for 48–72 hours before the chemotherapeutic treatment had a nonsignificant tendency towards a lower incidence of neutropenia and neuropathy than those who fasted for 24 h before treatment. In peripheral blood mononuclear cells, markers of DNA damage increased in all groups, although to a lesser extent in the extended fasting group [148].

Despite initial concerns about weight loss in patients with cancer receiving chemotherapy, no trials have revealed substantial loss of lean body mass or malnutrition due to IF [151]. IF was found safe and tolerable in an observational study of 28 children with type 1 diabetes with diverse cancers undergoing treatment during Ramadan [152]. In a case series, IF before and after chemotherapy was reported to be secure and well-received in 10 patients with a variety of cancers [153]. Finally, in another clinical trial, 25 patients with head or neck cancer undergoing chemotherapy were assigned to either a short-term fasting diet followed by a standard caloric diet, or a standard caloric diet followed by a short-term fasting diet [154]. Those patients fasted for 36 hours before treatment and 24 hours thereafter, having a total of 350 calories per day. Within 8 days of chemotherapy, no substantial weight loss was recorded, although there was an improvement in quality of life and weariness. Such benefits, in contrast, were not seen while having a regular diet [154].

Despite the limited clinical evidence currently available, several ongoing clinical trials are exploring the potential benefits of IF in various advanced cancer scenarios [146]. However, data on the specific nutritional interventions applied in these clinical trials remain incomplete and inconsistent. This includes details on nutritional guidelines, meal quality, and specific foods included in the diets. Comprehensive and standardized information on these aspects is critical to assessing the efficacy and feasibility of IF as a therapeutic strategy in cancer treatment. Further rigorous and well-designed clinical trials, especially, in subjects with obesity, are needed to provide conclusive evidence on the role of IF in cancer treatment and survival.

Recommendations:

IF may benefit cancer patients such as those with glioma or early-stage breast cancer, showing improvements in biomarkers like HbA1c and insulin resistance, and potentially reducing side effects during chemotherapy (Fig.3). Possible minor side effects include fatigue, headache, and

dizziness. While IF generally does not cause significant weight loss or malnutrition, ongoing monitoring is essential. IF typically involves minimal caloric intake (e.g., 500 kcal/day) during fasting periods, with unlimited calorie-free beverages. TRF limits calorie intake to specific hours, but detailed macronutrient composition varies and should be adjusted to individual needs.

5. Micronutrient deficiencies in subjects with obesity and cancer and recommended supplementation

Certain micronutrient deficiencies have been implicated in the development of obesity and are frequently present in individuals with obesity, including vitamins (A, B, C, D, E, folic acid) and minerals (iron, zinc, magnesium, selenium, copper, iodine, calcium and phosphorus) [155]. Potential mechanisms linking such micronutrients deficiencies with obesity involve dysregulation of carbohydrate and fat metabolism, dysfunction of pancreatic β-cell and abnormalities in the insulin-signaling cascade [155]. Since most micronutrients serve as enzyme co-factors in the body, thus regulating several metabolic processes, their deficiencies can lead to the development of severe health problems (apart from obesity), including cardiovascular diseases, immune dysfunction, osteoporosis, defective antioxidant defense mechanisms, neurodegenerative disorders and cancer [155].

Focusing on cancer, it has been recognized that nutritional status can greatly influence cancer development and progression [156], as well as anti-cancer treatment efficacy: both inadequate diet and cachexia can be present and negatively affect clinical outcomes [1]. Malnutrition is the main cause of inadequate micronutrient status in cancer patients, since macronutrients serve as “the natural carriers” of micronutrients [157]. However, apart from malnutrition, it is important to consider that cancer patients (especially with obesity) may require higher amounts of micronutrients due to their diseases-related pathophysiological, inflammatory and metabolic changes. Furthermore, the side effects of radio- or chemotherapy (e.g., loss of appetite, aversion to certain foods, alterations in taste, diarrhea or vomiting) can contribute to micronutrient deficiencies [157]. On the other hand, the presence of micronutrient deficiency can adversely impact disease prognosis, the effectiveness of cytoreductive therapy, and the risk of complications (such as depression, fatigue, delayed wound healing and impaired immunocompetence) [157]. Indeed, there has been some evidence on the potential beneficial effects of certain vitamins (A, B, C, D, E, K) and other micronutrients (copper, zinc, selenium, magnesium) on cancer prevention and treatment via their antioxidant, anti-inflammatory, and anti-apoptotic properties [158].

Based on the above associations, individuals with obesity (with or without cancer) should be screened for micronutrient deficiencies [158]. In the case of individuals with obesity and cancer, micronutrient supplementation should be considered in clinical practice, focusing on improving the outcomes of their standard therapy, as well as potentially minimizing the adverse effects of both cancer and anti-cancer treatment. Indeed, there are studies reporting the beneficial effects of the supplementation of certain micronutrients (mainly those with immuno-stabilizing and antioxidant properties, such as selenium, vitamin C and D) in cancer patients, as mentioned above. Administration of micronutrients with little storage or reserve capacity (such as folic acid, vitamin C, vitamin B12) is also clinically important [158].

The American Institute for Cancer Research (AICR) does not recommend the use of supplements for cancer protection [159]. The latest World Cancer Research Fund (WCRF)/AICR Third Expert Report on Diet, Nutrition, Physical Activity, and Cancer discusses the evidence on micronutrient intake and cancer risk [160]. For example, although there is strong evidence that consuming calcium supplements may help to protect against colorectal cancer, there is limited

data that dairy products might increase prostate cancer risk, and thus no recommendations have been made [160]. Also, there is limited-suggestive evidence that multivitamin supplements and vitamin D may decrease the risk of colon cancer, whereas there is limited-inconclusive evidence that folic acid, vitamin A, vitamin B6, vitamin E and selenium intake can reduce colon cancer risk [160]. Overall, this WCRF/AICR report does not recommend high-dose supplements for cancer prevention, but rather suggests that all attempts should be made to obtain the needed nutrients through dietary sources before prescribing supplements [160].

Healthcare professionals must collaborate to identify individuals at risk of micronutrients deficiencies, manage imbalances, and promote evidence-based nutrition guidelines, emphasizing on diverse diets and cautious supplementation [161]. According to the AICR, daily multivitamin/mineral supplement intake should be within the range of the recommended daily allowance (RDA) [157]. The RDA for several micronutrients can be found in ref [161]. Therefore, in the presence of micronutrient deficiencies that cannot be covered by diet (e.g., due to malnutrition or adverse events from the anti-cancer therapy), individuals with obesity and cancer may take a multivitamin/mineral supplement based on the RDA.

Certain recommendations for clinical practice could be made, especially for vitamins D and C, as well as selenium. For example, it is recommended to monitor vitamin D status in all cancer patients and treat any deficiencies by adequate vitamin D supplementation, i.e., 40-60 IU vitamin D/kg/day with a 25(OH)D target value of 100-150 nmol/L (40-60 ng/mL) [157]. Vitamin D deficiencies are particularly frequent in cancer patients with poor nutritional status, those treated with bisphosphonates, aromatase inhibitors, and chemotherapy regimens (e.g., taxanes, anthracyclines, and monoclonal antibodies), as well as in cases of muscular disorders, cancer-related anemia, cachexia and fatigue.

The Physician Data Query (PDQ) cancer information summaries for health professionals can provide evidence-based data regarding the use of high-dose vitamin C in cancer patients [162]. In this context, intravenous ascorbate administration has been reported to rarely exert adverse events (e.g., hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency-G6PD and oxalate nephropathy). Thus, G6PD laboratory testing should always be assessed before a vitamin C infusion. Both parenteral or oral administration of vitamin C supplements could be useful in the presence of poor nutritional condition, fatigue, cachexia or delayed postoperative wound healing [157]. However, the FDA has not approved the use of high-dose vitamin C as a treatment for cancer [162].

Regarding selenium, efforts should be made to achieve the optimal serum selenium level of 130 to 150 μg/L. However, patients with serum selenium concentration of ≥122 μg/L should not be supplemented with selenium [157]. It should be noted that serum selenium may reduce the toxicity of chemo- and radiotherapy and thus certain centers administer sodium selenite (i.e., the preferred selenium salt in oncology) as pre-medication before chemotherapy (e.g., 1 mg sodium selenite in 100 mL 0.9% NaCl) [157].

There is limited evidence that L-carnitine may beneficially affect the cancer anorexia-cachexia syndrome. Oral supplementation of l-carnitine may be helpful in malnourished cancer patients, as well as in patients on chemotherapy regimens that induce carnitine deficiency (e.g., ifosfamide and cisplatin) or peripheral neuropathy (e.g., taxanes) [157].

According to the PDQ cancer information summaries, the administration of vitamin A, vitamin C, vitamin E, a multivitamin (containing folic acid, vitamin B6, and vitamin B12) or beta-carotene did not affect breast cancer incidence or progression [163]. Similarly, beta-carotene or vitamin E

supplementation did not protect against lung cancer [164], whereas beta carotene, vitamin E, vitamin C and selenium intake did not affect the progression or regression of gastric cancer [165]. In contrast, a previous large randomized placebo-controlled trial (i.e., SELECT; n=34,887 healthy men) of vitamin E (400 IU/d of all rac-α-tocopheryl acetate) and selenium (200 μg/d from L-selenomethionine) supplementation not only failed to decrease prostate cancer incidence, but also reported an increased risk of prostate cancer with vitamin E administration [166]. Obviously, there is still a need for further research in this field.

Interestingly, several studies reported an increased dietary supplement intake among cancer patients. For example, among 2,772 US cancer survivors and 31,310 individuals without cancer from the NHANES 2003-2016, cancer patients reported a higher prevalence of any dietary supplement use (70.4 vs. 51.2%), multivitamin/mineral supplement intake (48.9 vs. 36.6%) and supplement use of 11 individual vitamins and 8 minerals compared with individuals without cancer [167]. The most frequently used supplements for individual vitamins/minerals were vitamin C, D, E and B12, as well as calcium. However, cancer patients reported lower amounts of nutrient intake from foods than individuals without cancer [167]. It should also be noted that nearly half of the cancer patients used dietary supplements without previously consulting their health-care providers, thus highlighting the need for discussion on dietary supplement use between physicians and cancer patients in daily practice during clinical visits [167]. Similarly, another cross-sectional survey among 1,217 ambulatory cancer patients found that 47.2% of them reported using dietary supplements: calcium and magnesium supplementation was most often reported followed by botanical and herbal supplements, multivitamins, vitamin D and the vitamin B group [168]. Of note, 41.5% of the supplement users started the use after cancer diagnosis, whereas 37.1% of them had used the supplements regularly and 19.2% sporadically before cancer diagnosis [168]. A previous systematic review evaluating dietary supplements use among patients with cancer (n=65 studies) reported that majority of the studied supplements (for example, vitamins, omega-3 fatty acids and botanicals) were found to be safe [169].

Based on all the above data, a complementary oncological treatment should include nutrition therapy and laboratory-validated supplementation of micronutrients. In this context, clinicians should discuss openly with individuals with obesity and cancer about nutritional supplementation, since several patients may be already on supplements, without the knowledge of their physicians [157]. Nutritional supplementation should be tailored and individualized based on each patient's diet, genetics, cancer type and treatment [157]. There is still a need for further evidence to establish global recommendations on micronutrient intake in individuals with obesity and cancer. Additionally, the clinical use of micronutrients supplementation to prevent cancer development remains to be elucidated.

Recommendations

Priority should be given to obtaining micronutrients from food sources rather than supplements. Daily supplements, if needed, should stay within recommended daily allowances, and high-dose supplements are discouraged. Monitoring and treating vitamin D deficiency is advised, along with maintaining optimal selenium levels, particularly in cancer patients. Specific supplements like sodium selenite and L-carnitine may be considered in targeted cases, while high-dose vitamin C lacks FDA approval as a cancer treatment. During chemotherapy or radiotherapy, it is recommended to avoid antioxidant supplements in doses above tolerable limits.

6. Conclusion

The adoption of a healthy, balanced diet, rich in plant-based foods has been related to a reduced risk of developing various types of cancer [5]. In particular, a high intake of dietary fiber, fruits, vegetables, pulses, whole grains, as well as a minimum consumption of alcohol and processed meat, with total restriction of sugar-sweetened drinks, are crucial for cancer prevention and treatment [6]. Although no clear nutritional indications are available in individuals with obesity and cancer, the MedDiet, has been correlated with a decreased risk of several cancers [6, 170]. Furthermore, there is a growing interest in the use of IF or KD as an adjuvant therapy in cancer treatment, but current evidence is scarce and thus no recommendations can be made [171].

On another issue, malnutrition along with the side effects of radio- or chemotherapy can lead to inadequate micronutrient status in cancer patients [172]. Furthermore, cancer patients (especially in the presence of obesity) may require higher amounts of micronutrients due to their diseases-related inflammatory, pathophysiological, and metabolic changes [173]. On the other hand, micronutrient deficiencies may adversely affect cancer prognosis and the efficacy of cytoreductive therapy [172]. Having said that, there has been some evidence on the potential beneficial effects of certain vitamins (A, B, C, D, E, K) and other micronutrients (copper, zinc, selenium, magnesium) on cancer prevention and treatment via their anti-apoptotic, anti-inflammatory and antioxidant properties. Administration of micronutrients with little reserve or storage capacity (such as folic acid and vitamin B12) is also clinically significant.

Overall, individuals with obesity and cancer should be screened for micronutrient deficiencies. Although, the AICR does not recommend supplement use for cancer protection, if micronutrient deficiencies exist and cannot be corrected by diet (e.g., due to adverse events from the anti-cancer therapy or malnutrition), individuals with obesity and cancer may be administered a multivitamin/mineral supplement based on the RDA [159]. Certain recommendations for the supplementation of vitamins D and C, as well as selenium have been made. In clinical practice, a complementary oncological team should include registered dieticians that can provide medical nutrition therapy and laboratory-validated supplementation of micronutrients.

Statements

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

G.M. conceived of the presented idea. L.B., S.B., M.E.G., N.K., L.T. and L.V., wrote the draft of the manuscript. G.M., A.C., L.B., V.Y. and M.H. review the manuscript.

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Figures Legends

Fig. 1. Favourable mechanisms of the Mediterranean diet in the patient with obesity and cancer.

Fig. 2. Favourable mechanisms of the Ketogenic diet in the patient with obesity and cancer.

Fig. 3. Favourable mechanisms of the Intermittent fasting in the patient with obesity and cancer.