July-Sept 2022| Vol. 2 Iss. 3

& Developmental Adolescent Health

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Journal of the Hellenic Society of Adolescent Medicine – J.H.S.A.M.
(Committee of Developmental and Adolescent Health)
www.youth-med.gr

Quarterly Scientific Publication of the Hellenic Society of Adolescent Medicine
(Committee of Developmental and Adolescent Health)

& Developmental Adolescent Health

2JYLY-SEPT 2022 | Volume 2, Issue 3

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PUBLISHER/OWNER
Hellenic Society of Adolescent Medicine
174 Kifisias and Veaki 2, 11525, Athens E-mail: info@youth-med.gr
Print ISSN
2654-1858
Online ISSN
2732-8376

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Figure 1. Diagrams describing the height of the participating adolescents, (a) boys, (b) girls

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Editorial

Dear colleagues,

the third issue of Volume 2 of the Journal Developmental and Adolescent Health (JDAH), is dedicated to reviews concerning multiple aspects and risk factors of pediatric and and adolescent cancer.

There is a review article investigating children's nutrition and the risk of developing neoplasms in childhood and adolescence. Another review article is focusing on mobile health features for adolescents and young adults with cancer diagnosis, while these is also an article discussing the design strategies for the development of mHealth services. The forth review article is highlighting the pregnancy eating habits and risk of tumor appearance in descendants in children and adolescents.

We hope that you will find interest in our new issue, which offers valuable original findings and important information about hot topics concerning adolescent health, especially during the pandemic era.

On behalf of the editorial team and content management of JDAH,

Artemis K. Tsitsika MD, PhD
As. Professor in Pediatrics-Adolescent Medicine
Head of the Adolescent Health Unit (A.H.U.)
Chair of "Str. Of Developmental & Adolescent Health" MSc
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President of the Hellenic Society for Adolescent Medicine/Health
Editor in Chief of the Journal of Developmental & Adolescent Health (JDAH)

Children's nutrition and the risk of developing neoplasms in childhood and adolescence.

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ABSTRACT

Background: The effect of children's eating habits on the development of cancers in childhood and adolescence has been of great concern to researchers in recent years. This literature review aims to present the foods that may be related to the prevention or the incidence of cancer at the children between 0-18 years of age.

Methods: A research on nutrition and the appearance of tumors in children and adolescents between the ages of 0-18 years old was done regardless of gender, educational level and nationality. A literature review was conducted using online databases and words, such as "Nutritional Habit", "Nutritional Status", "Diet'', "Adolescence'', "Childhood'', "Pediatric Cancer'', "Neoplasm'', "Carcinoma'', "Lymphoma'' and "Leukemia''. We collected and analyzed a total of 34 surveys, including three meta-analyses, ten case-control studies, one cross-sectional study and two research articles.

Results: Worldwide the results showed a protective interrelation between breastfeeding, and the consumption of fruits, vegetables and dairy products in the development of childhood cancer. In contrast, the consumption of meat, cured meats, smoked fish, vegetable oils, soft drinks such as cola, junk food, but also the exposure to heavy metals, stand as the risk factors for childhood cancer cases.

Conclusion: The Disease's prevention is associated with intrauterine life and the mother's diet during pregnancy. The nutrition of the child is crucial in the first years of life and eating habits then affect food choices at an older age. A Balanced children's nutrition is important and depends on the parents who should consult health care professionals. Finally, due to the constant appearance of new data, it is considered necessary to further study this field in Greece and cross-culturally.

Key Words: *Childhood, Adolescence, Cancer, Leukemia, Nutrition*

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Introduction

Cancer is the second most common cause of death in children aged 1-14 years after accidents. About 10,470 children in the United States under the age of 15 will be diagnosed with cancer in 2022, and the number of deaths is 1.050 children under the age of 15. Pediatric cancer rates have been rising more slowly in recent decades due to significant advances in treatment, resulting in 85% of children with cancer surviving 5 years or more. However, survival rates can vary depending on the type of cancer and other factors, such as the location of the tumor in the body, the stage of cancer, and its growth rate (1).

More specifically, the most common types of children's cancer are different from those adults suffer from, with the main ones being: leukemia, brain, and spinal cord tumors, neuroblastoma, Wilms tumor, lymphoma (including Hod and non-Hodgkin), rhabdomyosarcoma, retinoblastoma and bone cancer (including osteosarcoma and Ewing sarcoma) (1).

Leukemia, a bone marrow and blood cancer, is the most common type of childhood cancer and accounts for about 28% of all cancers in children. The main symptoms are pain in the bones and joints, fatigue, weakness, pale skin, bleeding or bruising, fever, and weight loss. The most common types are acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) (1), with ALL accounting for about 80% of pediatric leukemias, occurring in children 2-5 years of age, more common in boys where a poorer prognosis occurs, especially in Caucasian and Hispanic populations (2-4).

Risk factors for childhood cancer include genetic predisposition, syndromes such as Down Syndrome, exposure to viruses such as Epstein-Barr Virus (EBV), pesticides, dyes, air pollutants, petroleum solvents, ionizing radiation, parent's habits such as smoking and diet, and finally the nutrition of children from the time of birth (5,6). Specifically, the diet has been linked to the occurrence of various types of cancer in both children and adults (7). This is explained by biological mechanisms, like exposure to mutations that lead to a lack of nutrients and micronutrients. These dietary factors are necessary to protect against cancer by supporting cellular integrity, reducing inflammation, and improving the immune response (8-10).

In addition, certain types of food, such as cured meats and smoked fish contain precursor forms of N-nitroso, leading to the formation of carcinogenic compounds N-nitroso in gastric acid (11).The molecular action of these compounds is inhibited by antioxidants such as vitamins C, E, flavonoids found in fresh fruits, vegetables, green tea, and soy (12-14). At the same time, the Mediterranean diet has a protective effect against chronic diseases including different types of cancer, through its anti-inflammatory and antioxidant action (15). Finally, breast milk contains several active immune components and multifactorial anti-inflammatory defense mechanisms, that affect the development of the immune system of the breastfed infant. A the same time, this type of feeding transfers to the newborn secretory IgA antibodies (6) and prebiotics (16). Biological mechanisms, such as the gut microbiome of the newborn, Natural Killer cells, and stem cells in breast milk can elucidate the inverse relationship between breastfeeding and leukemia. On the contrary, the introduction of infant formula into the child's diet modifies the intestinal microbiome and cannot mimic the protective properties of breast milk (6).

MATERIALS AND METHODS

A research algorithm was created in order to extract data on the effect of children's eating habits in the appearance of neoplasms in childhood and adolescence worldwide. Scientific online databases (PubMed and Google Scholar) were used to complete the research of this review. The main inclusion criteria were: a) age group:0-18, b) no geographical restrictions, c) type of study: cross-sectional, case-control, systematic reviews and meta-analyses and d) language: English. Finally, the authors collected and analyzed a total of 34 surveys, of which three meta-analysis, ten case-control studies, one cross-sectional study, and two research articles.

RESULTS

Breastfeeding

Starting with breastfeeding in a meta-analysis by Kwan et al. in 2004 (17) in the USA 14 case-control studies were studied and a negative correlation was found between long-term breastfeeding (> 6 months) and ALL as well as with AML. At the same time, short-term breastfeeding (<6 months) was found to be equally protective for the occurrence of ALL and AML in childhood, while the socioeconomic level as a confounding factor did not seem to affect the results. Another similar meta-analysis was conducted by Amitay et al. in 2015 (6), including 17 studies of cases and controls. The authors have concluded that compared to zero or less than 6 months of

breastfeeding, any for 6 months or more was associated with 20% fewer Odds for childhood leukemia, while continuous breastfeeding compared to the absence of it leads to 9% lower Odds.

In addition, in a case-control study by Schraw et al. involving 142 cases and 284 controls aged <14 years, the correlation between infant feeding practices and the age of solid food intake with a risk of acute lymphoblastic leukemia in childhood was studied. The results demonstrated that the longer duration of nutrition with formula and the delayed induction of solid food is not related to an increased risk of ALL (18). In contrast, in the case-control study by Greenop et al. (19) in 2015, 322 ALL cases, 679 ALL controls, 299 CBT cases, and 733 CBT controls participated and was found that breastfeeding, regardless of the duration, was linked to reduced risk of ALL. The study also showed that formula intake within 14 days of birth affected positively ALL, as was exclusive formula feeding for up to 6 months and found no significant difference between breastfeeding or formula feeding and the risk of brain tumor (30). Finally, in another study of Lupo et al. in 2014, 322 RMS cases and 322 controls participated and concluded that breastfeeding ≥12 months is significantly connected to a reduced risk of childhood retinoblastoma (RMS) (16).

Milk and Dairy Products

Other categories of food studied for association with ALL were meat and dairy products, as shown by a case-control study by Diamantaras et al. in 2013 in Greece. A total of 139 cases of infants' leukemia participated in this study, of which 121 were acute lymphoblastic leukemia and came from the Nationwide Registry for Childhood Hematological Malignancies. The same number of controls as the cases was used, from the same institution where the children were hospitalized for minor diseases and negative history of cancer or nutrition/metabolic disorders. The study was performed through interviews with the care givers and the children. A significant relation was found between the consumption of milk and dairy products and ALL, especially in the first year of life. This result arises probably from the action of vitamin D and the proteins that milk and dairy products contain. On the contrary, higher consumption of additional fats (butter, margarine, etc.) increased the risk of childhood leukemia, while a marginally statistically significant correlation with ALL was observed in macronutrient proteins. Finally, the study showed no statistically significant upregulation of risk between other foods and macronutrients studied with ALL (cereals, fruits, vegetables, meat, fish, and nuts) (20).

Meats

In a case-control study by Peters JM et al. in 1994, an attempt was made to determine the relationship between foods containing N-nitroso precursors or are inhibitors of the substance, and the occurrence of leukemia. The study included children aged 0-10 years living in Los Angeles, and the mother provided the researchers with information on the frequency of eating certain foods over a specific period. A significant effect was found with hot dog consumption, demonstrating that including more than 12 hot dogs per month in a child's diet significantly increases the risk of childhood leukemia (21). Sarasua S. et al. in 1994, conducted a case-control study regarding the effect of broiled and cured meat on childhood cancer. The study involved children aged 0-14 years and examined the frequency of consumption of ham, bacon, hot dogs, hamburgers, bologna, pastrami, corned beef, or salami and broiled food. The results showed that ALL was related to hamburger consumption, specifically eating more than one per week and a link was also demonstrated between brain tumors and feeding the child with ham, bacon, and sausage, and hot dogs, specifically more than 1 hot dog per week (22). At the same time, this study exhibited that the combination of no vitamin intake and meat consumption had a strong effect on ALL and brain neoplasms. A subsequent case-control study by Liu CY et al. in 2009, addressed the association between the consumption of cured/smoked meat and fish, which are the main sources of exposure to nitrites and nitrosamines, and the occurrence of acute childhood leukemia. The survey was aimed at people aged 2-20 years and a total of 179 cases and 475 controls participated. The questionnaire given could be completed either by the individual or by his/her mother and concerned the frequency of consumption of fruits, vegetables, bean-curd foods, tea alcohol-containing beverages, cured/smoked meat or fish, and pickled vegetables. This study displayed that eating cured meat and smoked fish more than once a week was related to an increased risk of ALL. No significant difference was found between consumption of tea, fruit, and pickled vegetables and acute childhood leukemia (23).

Oils

One category of food that has been of interest to researchers is vegetable oils. Particularly, an analysis with one variance of a case-control study by Lubin F.et al. in 2000, showed that high consumption of vegetable fat, carbohydrates, and vitamin E were significantly

correlated to the risk of brain tumors in children (24). Similar results were also shown in a study of cases and controls by Diamantaras AA et al. in 2013 in Greece, which studied the link between childhood leukemia with the consumption of macronutrients, various foods, energy intake, and the Mediterranean diet's consumption. In this study children aged 5-14 years were included and was found that higher consumption of added fats, such as seed oil and olive oil, was connected with an increased risk of childhood leukemia (20).

Junk Food

The scientific community has also shown particular interest in studying the effect of cola and junk food on childhood cancer. Specifically, a meta-analysis by Thomopoulos et al.in 2015 in Greece, with 12 case-control studies, concluded that the child's consumption of cola-type products did not correlate with the occurrence of ALL (25). On the other hand, a case-control study by Ayub et al. in 2020 found that the consumption of junk food and caffeinated beverages increased the risk of childhood leukemia, as children with a leukemia diagnosis who participated in the study had a higher consumption of these foods (26).

Fruits and Vegetables

Several studies have emphasized the effect of fruits and vegetables on the incidence of childhood leukemia, mainly because of their protective properties. A case-control study by Kwan ML et al. in 2004, attempted to highlight the relationship between the foods consumed by a child in the first two years of life and the development of leukemia. This study presented that frequent consumption of oranges and bananas, as well as orange juice, decreases the risk of childhood leukemia (27). Both fruits are important sources of vitamins and minerals, such as vitamin C and potassium, preventing carcinogenesis and protecting against DNA oxidation (28).

Heavy Metals

Researchers have focused also in recent years on the effect of heavy metals in the development of childhood cancers, both through their intake through the digestive tract, and through the air and percutaneous contact (29). A study conducted off the coast of China showed that farmed scallops contained significant amounts of heavy metals. In particular, high levels of cadmium (Cd), arsenic (As), and nickel (Ni) were found, being public health concern due to the increased risk of cancer if consumed (30). Another study in Nigerian communities with heavy artisanal mining activity looked at the health risks of eating heavy metal-contaminated vegetables. More precisely, consumption of vegetables contaminated with cadmium (Cd) and chromium (Cr) can lead to an upregulated risk of childhood cancer (31).

DISCUSSION

The main goal of this research was to examine the possible foods that may influence the occurrence of childhood cancer. More specifically, the eating habits that appeared to protect against childhood cancer were breastfeeding for at least 6 months (6,16,17,19), consumption of dairy products (20), as well as fruits, vegetables (27) and tofu (23). Some studies have shown that formula feeding leads to an increased risk of childhood cancer (6,19), while in a study of cases and controls, longer duration of formula feeding and delayed introduction of solid food were not associated with an increased risk. On the other hand, the types of food which were associated with childhood neoplasms were hot dogs (21,22), hamburgers (22), cured meats, smoked fish (23), and high amounts of vegetable (24) and added fats (20). Also, high-risk are considered to be caffeinated beverages and junk food (26), as well as the intake of heavy metals through food (29-31).

The prevention of cancer's development commences in the endometrial life and with the diet of the mother during pregnancy. The children's diet during the first years of their life plays an important role, as according to scientific studies, eating habits are established in the first years of life and affect food choices at an older age. For this reason, it is vital for parents, in cooperation with health professionals, to introduce solid foods and potential allergens into the child's diet promptly and encourage children to consume a variety of foods, especially foods rich in iron and zinc (32).

In regard to breastfeeding, the guidance of the World Health Organization is to follow exclusive breastfeeding for the first 6 months of life, to achieve the optimal growth, development, and health of the infant. Newborns who are not breastfed or have mixed feeding are considered a high-risk group for malnutrition, morbidity and mortality (33). Finally, according to the recommendations of experts, soft drinks containing caffeine, as well as honey and unpasteurized foods should be avoided at ages younger than two years (32).

CONCLUSION

In summary, the model of nutrition followed during infa-

-ncy and adolescence, as well as the habits and knowledge available to caregivers, are of great importance. Some eating habits that protect the appearance of cancer in childhood and adolescence, are the consumption of fruits and vegetables, legumes, and cereals. The reduced intake of foods with a high percentage of sugar and salt, soft drinks and alcohol, as well as red meat is also considered protective(34).

The contribution of society and government in taking measures to promote and support healthy eating can be particularly beneficial. Specifically, it is essential that young parents can receive objective and comprehensive information in appropriate feeding practices, without the influence of advertising. Moreover, it is necessary to support young mothers, both socially and professionally, so that breastfeeding and childcare can continue unhindered even after their return to paid employment. It may also be beneficial to create support networks among mothers in the community, to interact with each other, and involve counsellors to whom mothers can be referred from hospitals and clinics. Finally, it is extremely important to ensure that the quality of products placed in the market follows health protocols and is suitable for feeding infants and young children (33).

It is also necessary to educate and raise awareness among children and adolescents, parents and grandparents, as in many cases they seem to have a negative impact on the eating habits of their grandchildren (35). High attention should be given to specific social groups, which appear to be more vulnerable and exhibit high-risk behaviors, such as sexual minorities (36). Studies have shown that obesity and overweight problems, physical inactivity, diets low in fruit and vegetables are significantly more prevalent among sexual minority individuals than heterosexual women. In addition, care is also reserved for families of low socioeconomic level, for whom government programs in the U.S. have been put in place so that they have access to nutritious meals and educational activities that support the healthy eating habits of children and adolescents (32). In Greece though, young parents can visit specific sites to get consultation on proper children's nutrition from the time of birth to adulthood to establish proper eating behaviors (37).

In conclusion, this literature review summarizes the foods that may protect or lead to children's cancer but future research is needed to establish all the types of food that may be related to pediatric neoplasms.

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A review of mobile health features for adolescents and young adults with cancer diagnosis

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ABSTRACT

Adolescents with cancer seem to be a population with special needs for treatment and support as significant physical, cognitive, and psychosocial changes take place at this developmental stage. Interventions via portable and easily accessible devices have proven to be effective in dealing with health-related problems. Adolescents, due to their inherent ability to operate modern technological devices, could benefit from mobile health (mHealth) applications pointing out the necessity of their integration into medical practices and public health. After reviewing 40 articles, it appears that mHealth practices have the potential to overcome some of the obstacles that arise during the treatment process, aiming at optimal symptom management, better treatment outcome and therefore improvement in adolescents' quality of life. MHealth interventions in the field of adolescent cancer, can offer services such as recording symptoms, improving communication with health care staff, enhancing adherence to therapy, accessing valid sources of information, providing social support, and implementing training in the management of distressing symptoms. This review concludes possible limitations and future research proposals underlying the need of creating a mHealth application that incorporates the aforementioned features.

Key Words: *mobile health, mHealth, adolescents, young adults, cancer, application features .*

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Introduction

Adolescent cancer

Adolescence is a special period, presenting unique developmental and psychosocial characteristics while being the age milestone between childhood and adulthood (1). The World Health Organization (WHO) defines adolescents as people aged 10-19 years old while recognizing that this range is fluid, as it varies by gender, biological, cultural, and socioeconomic factors (1). Every year, around 14,000 cases of adolescents and young adults with cancer are recorded in Europe (2). This population has unique care needs and requires individual support from the time of diagnosis, during medication, and after the cure, as cancer survivors (2).

Clearly, adolescence is characterized by significant physical and cognitive changes along with critical psychosocial challenges, related to self-identity, relationships with peers, development of autonomy, sexuality and future goal-setting (3,4). As a result, adolescents with cancer face more challenges (2). More specifically, prolonged hospitalization in combination with treatment side effects (e.g. hair loss, weight gain, scarring, infertility and amputation) often influences adolescents in terms of body image, health system confidence and self-esteem (2).

Mobile Health

WHO defines Mobile Health (mHealth) as "the medical practice and public health practice supported by mobile devices such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices" (5). It also includes the use of mobile and wireless applications (e.g. SMS text messages, applications, mobile devices and the use of social media) to provide health-related services (6). MHealth devices seem to be widespread, especially in children and adolescents, as supported by the meta-analysis of Ramsey et al. (7) which showed that 95% of adolescents reported owning or having access to a mobile phone, 73% to a smartphone and 87% to a desktop or laptop. Recent evaluations estimated that 95% of 13-17 years old own or have access to a smartphone, which they often carry with them and use regularly in order to stay connected (7). Regardless of the increased growth of mHealth applications, it is surprising that only a quarter of downloaded applications is being used just once (8). It is noteworthy that populations from lower socioeconomic status appear to have limited access to them, using smartphones up to 25%, a fact that could create selection bias, in terms of the benefits of mHealth interventions (9).

Key features

Symptom tracker

There is evidence that daily symptom monitoring is beneficial for 5–18 years old newly diagnosed cancer patients, providing early symptom recognition and proper medical response (13). Bradford et al. (14) in their research supported that when the recording of symptoms was inadequate, the rates of discomfort and unnecessary hospitalization appeared to increase (14). Deficient symptom control seems to influence medication tolerance, leading to long-term issues, and adversely affecting the quality of life both of the patient and his family (14). Current practices in symptom assessment required patients' accurate recall after one to six weeks during medical visits (15). Furthermore, in most cases, the frequency and severity of symptoms appear to be underestimated, resulting in discrepancies between self-reports and medical records (10). Correspondingly, a broad percentage of patients' symptoms and difficulties remain unspecified provoking difficulties in treatment (10). Finally, poor symptom management has been shown to be associated with the onset of Post-Traumatic Stress Disorder and other psychological problems (13).

Pain-related symptom tracker

Fortier et al. (16) at their study found that 100% of children diagnosed with leukemia, the most common diagnosis of childhood cancer, report pain during the first year (16). The feeling of pain, in particular, may come from the underlying disease, but for most children, it is iatrogenic or caused by the treatment itself (16). Acute pain requires immediate intervention, as its underestimation can lead to chronic pain, increasing its levels while limiting the patient's subsequent cooperation during medical visits (17). Cancer-related chronic pain is also accompanied by a variety of negative consequences such as high rates of functional disability, emotional and behavioral difficulties (e.g. anxiety and fear), parental anxiety, barriers to disease recovery, reduced sleep, and poorer overall quality of life.(2,17). MHealth services have the opportunity not only to improve but also to enrich pediatric pain management by providing developmentally appropriate and attractive delivering methods (2).

There is evidence that parents who are in charge of their children's treatment at home appear to under-treat the pain symptoms, despite the availability of

effective pharmacological and non-pharmacological interventions (12). In particular, in the study of Simon et al. (12), which included cases with clinically significant levels of pain presented that one-third of children receiving chemotherapy were not given analgesics at home (12). Pain management is a significant cost burden for the healthcare system, therefore it is necessary to find innovative treatment methods for chronic pain, with mHealth technologies being a promising alteration (12,18).

Communication with medical staff

Effective communication between doctors, patients and parents serves a significant role as it seems to enhance patients' sense of satisfaction and treatment compliance thus improving its outcome (10). As a matter of fact, the same researchers reported that the main factor for non-compliance with treatment in young patients is poor communication between doctors, patients and parents (10). Therefore, it becomes crucial to create new, alternative methods of communication, with the aim of providing patients both support and counseling for the management of distressing symptoms (10).

Adherence to treatment

The urge for autonomy and the neurodevelopmental changes that arise throughout adolescence (e.g. development of executive functions) are contrasted with the indicated adherence to treatment (19). As noted by Ross et al.(20) children with cancer appear to take responsibility over chemotherapy without being provided with the necessary medical supervision (20). There is evidence that non-compliance with the treatment plan could lead, on the one hand, to complications in the patient's health, and on the other hand to imminent death (20). Specifically for AYAs with chronic diseases, relatively low compliance with medication appears to be observed, bringing them into focus on establishing innovative programs for treatment plans (20).

Information provision

Proper information provision could moderate the distressing symptoms of treatment, during both the therapy process and the follow-up period (21). Mobile health interventions offer cancer patients the ability to manage the barriers occurring during treatment by providing information and training in self-care skills (22). Furthermore, providing information and education to patients and their parents can improve the experience of the disease as well as clinical outcomes (10). More specifically, it has been argued that knowledge enhance-ment is associated with reduced levels of stress in patients and their families, improvement of side-effects control and therefore reduction of symptoms severity (10).

Social support

Feelings of isolation may occur throughout the cancer trajectory and there has been an association between the absence of social support among cancer patients with poorer physiological and physical functioning, greater psychological distress, and reduced quality of life (23). A recent study indicates that cancer patients could benefit from web-based support interventions as they provide social encouragement and social bonding (24). As a result, adolescents with cancer had the opportunity to obtain healthier behaviours and obtain optimal ability to cope with illness outcomes and overall better psychological well-being (24).

Coping strategies

It is necessary to mention that adolescents during treatment are confronted with a variety of stressful experiences related to the disease and treatment, regarding the way they perceive the changes which occur and the urge to utilize appropriate behavioral and cognitive strategies in order to manage them (25). Furthermore, AYAs educated in self-management skills and coping strategies can monitor their health status, feel controlled and therefore experience less stress (2,26). Studies have shown that adolescents with a range of cognitive, behavioral, and emotional skills have the potential to maintain an optimal quality of life (2).

METHODS

The main purpose of this review is to search the existing features of mHealth interventions applied in adolescents and young adults with cancer. Bibliographical research was conducted focusing on any kind of adolescent cancer and mHealth interventions in various databases. Specifically, most of the included articles come from Scopus, Pubmed, and a few of them from Cochrane Library and W.H.O. The present review includes both adolescents and young adults respecting the wide age range of this developmental stage. The aforementioned research concluded in 40 articles, limited to the English language. Most of the articles were clinical trials while some of them were systematic reviews.

RESULTS

The present review indicates the most commonly used features of mHealth interventions implemented in the care of adolescents and young adults with cancer diagnoses.

The key features that our research detected were the following: symptom tracker, pain-related symptom tracker, communication with medical staff, adherence to treatment, information provision, social support, and coping strategies. More specifically, in this review communication with medical staff seemed to be highly important as it was the most frequently applied feature with 18 articles confirming it (4,9,10,12-14,17,18,20,21,25-29,36,39,40). Subsequently, also 17 studies included the feature of adherence to treatment (7,10-12,14-17,19,24-26,29,36,37,39,40). In addition, the symptom tracker was referred to 14 more articles (4,6,7,9,10,13,15,19,21,25,27,29,36).

Also, throughout literature there are more 14 studies encompassed the feature of information provision (4,7,9,10,12,18,21,24-27,29,36,40). Furthermore, pain-related symptom tracker was the following used feature with 13 studies confirming it (2,7,10,12-15,17-20,25,28). Also, the facility of social support was found in 13 researches (4,7,9,10,21,23-25,27,32-34,36,40). Finally, in this review, the least implied mHealth features was the feature of education in coping strategies that was included in 12 studies (2,7,11-13,17,18,20,25,28,35,40).

DISCUSSION

MHealth interventions can overcome some of the barriers related to adolescents' cancer treatment, hence improving their quality of life(10). Initially, the alternative solutions via electronic means could overcome some difficulties of face-to-face interventions, such as mobility limitations or patient's fatigue (11). It is also a fact that changes in treatment practices force children to spend less time in the hospital and more time at home (2). MHealth interventions have the ability to bridge this gap, as smartphones, for example, can be used in any place (e.g. home, school, hospital) and therefore provide real-time support (12). Pappot et al.(9) also argue that mobile devices have proved useful in populations of rural areas or lower socioeconomic groups, who may previously not have had access to health care interventions (9). In fact, mHealth services seemed to have been very effective in treating chronic diseases, especially during the period of the COVID-19 pandemic, when hospital access was limited (5).

Symptom tracker intervention

A valid mHealth intervention for the real-time symptom recording is the electronic calendars (eDiaries) offering the potential to minimize recall bias (14). In fact, patients often seem to positively evaluate the electronic recording of their personal health data because it is easier and more reliable compared to traditional paper methods and simple recall (15).

Self-reports, as well as real-time symptom recording, are considered the "gold standard" for assessing symptom burden (27). Vaughn et al. (27) in their research reported that pain, nausea, vomiting, fatigue, bleeding, diarrhea, headache, itching, sleeping difficulties, and rashes were the most commonly electronically recorded symptoms (14,27). In addition, patients could add specific components, such as the intensity and the exact time of each symptom, as well as interventions that would be applied, thus improving symptom understanding (15,27).

It is noteworthy that the symptom tracking feature in the Kraftværkæt application was the most frequently used with positive reviews from users, as it contributed to the daily reminder of events and symptom progression (4). Also due to this feature, the patient can provide an electronic medical history during the medical visit improving the overview of symptom progression (4). In a review of 62 studies that used electronic pain diaries, patients reported high levels of compliance to therapy (19). Factors that seemed to facilitate calendars' compliance included the smaller size, the provision of a user manual, and the reminders for tracking symptoms (19). The portability of these devices and the availability of voice messages may also enhance data entry compliance (19).

Pain-related symptom tracker intervention

Jibb et al. (2) at their research, indicated that adolescents with cancer would want to develop practical skills for managing their disease (2). Smartphone-based real-time support and access to pain self-management programs offer patients the opportunity to manage their own symptoms the moment they occur (2). Correspondingly, increased feelings of autonomy and self-efficacy are noted as important factors that seem to contribute to behavioral change and successful pain management (2,17). The eDiaries mentioned above can also contribute to the electronic collection of pain-related data, which could also be used by healthcare professionals to help optimize treatment plans and pain management interventions (17).

Communication with medical staff intervention

The implementation of mHealth interventions could bridge the gap between the hospital and the home context, as medical staff could be able to intervene, regardless of the patient's caring environment (12,13).

Passardi et al. (29) in an attempt to optimize communication between cancer patients and doctors created a mobile application for patients and a web dashboard for health professionals. In particular, it enabled the medical staff to enter details into the treatment plan, set medication reminders, monitor treatment compliance and medication's side effects, while communicating with patients through a secure messaging system (29). In addition, one more application enabled patients to evaluate pain symptoms in real-time while allowing medical staff to intervene either directly or not, based on the severity of the symptoms (10). Finally, a mHealth application that allowed the recording of pain symptoms in children with cancer used an algorithm to evaluate whether immediate intervention is needed and thus send an automatic email to the appropriate medical staff (20).

Adherence to treatment intervention

MHealth interventions, and in particular mobile applications, could increase commitment to treatment plans through well-designed and developmentally appropriate methods which can promote entertainment as well (17,30,31). For example, in their application, Mehdizade et al.(10) added a function similar to a diary with features such as reminders for future medical appointments as well as the medication timing, preventing parents' and patients' disorganization and thus contributing to optimal compliance with the treatment plan (10).

Information provision intervention

One of the most common methods of providing information to cancer patients is the oral presentation during the clinical visits but it is supported that 40-80% of them is either immediately forgotten or misremembered (10). MHealth services could overcome this barrier by providing information modules via searching categories as well as training on essential aspects such as the disease, the symptom management and its treatment process (10). Furthermore, Hunter et al. (18) indicated in their research a web-based intervention that delivers educational information, via interactive multimedia means including movies, games, and animation. The study of Simon et al. (12) showed that when the recording of the pain symptom was in lower levels, the application, as a first intervention, provided families psycho-educational information applicable to the home environment.

Social support intervention

This review shows that he social support application fea-ture enables AYAs with cancer to share and receive information about the disease, support each other and thus contribute to the quality of life improvement (10,32-34). Accordingly, some mHealth applications give the user the opportunity to have an experience similar to online forums, where adolescents with cancer communicate with other patients, share experiences related to the disease and its treatment thus creating a network of emotional support (10,32,34). Specifically, users felt supported through the exchanging of personal experiences while mHealth applications have the potential to reduce family's socio-economic burden and stress as they provide communication with organizations and social services (10,34).

Coping strategies intervention

Research indicates that several mHealth applications attempt to contribute to patients' empowerment, self-management, and family psychoeducation on pain management (12,24,26,35). According to Govender et al. (25) referring to mHealth video games, the goal of empowerment, resilience and self-management is achieved through the "positive" addiction of the user. They, also, argue that video games are an upcoming practice, as they function by enhancing stress-sensitive mental processes, giving positive feedback to stress-regulating neurotransmitters (26). Noteworthy, a Hunter et al. (20) study on a mHealth application in mobile phones provided effective training strategies and skills for pain management such as diaphragmatic breathing, gradual muscle relaxation, guided imagery, distraction and mindfulness, regardless of the patient's care environment (20,29).

Limitations and further research

Consequently, criticism has been reported regarding both the content and the validity of the aforementioned features of mHealth applications (36). Firstly, a detailed protocol encompassing both medical staff and AYAs was lacking in most of the apps, while even fewer have established their effectiveness and prosperity in a wider audience (27,36). This limited perspective and the fact that some of the included studies presented poor methodological analysis, create barriers in the generalization of the results to an expanded population (26,27). Furthermore, few mHealth apps have been judged for their deficient evaluation and their design process as AYAs' contribution was limited (9). Empirical and repeated testing of mentioned features, as well as the evaluation of different adolescent caring environments rather than the hospital (e.g. home and school), was inadequate (2,37).

Moreover, it is worth mentioning that most of the studies' outcomes were synthesized by statements of AYAs, willing to share (38). This comes as a natural result as AYAs are characterized by fear of rejection and social judgment or introversion towards cancer-related topics (38). Undoubtedly, the under-resourced population has restricted access to mHealth interventions, potentially resulting in selection bias (9,38). In conclusion, future research should implement testing of feasibility and acceptability of mHealth interventions in the target population contextually, while further investigation should be made on their usability in underprivileged populations (38-40). Forthcoming testing of the effectiveness of mHealth services could also consider the implementation of all the aforementioned features in one single application.

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Original Research

Design strategies for the development of mHealth services in healthcare of adolescents with cancer

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ABSTRACT

During the developmental stage of adolescence, profound physical, cognitive, and emotional changes occur, thus making adolescent cancer patients a population that seemingly have unique needs for support and treatment. Health-related difficulties have been effectively addressed by the use of portable and accessible technology interventions. Adolescents may benefit from mobile health (mHealth) applications that highlight the significance of their integration into medical procedures and public health, due to their innate capacity to use modern technology services. After reviewing 31 articles, it appears that well-designed mHealth practices have the potential to enhance the long-term devotion of the user to the received intervention. MHealth tools seem to incorporate widely applied theories such as Behavior Change Theory, User centered Design, Social Marketing Theory, Social Cognitive Theory, Self-Determination Theory and Narrative Transportation Theory, in order to increase patients' engagement with the main purpose of behavioral change. The aforementioned theoretical frameworks include engaging strategies such as developmentally accepted content, rewards, customization, user feedback, time-appropriate intervention delivery, multimedia provision, ease to use and therapeutically designed games that could be implemented in mHealth interventions for adolescents with a cancer diagnosis. Both the theoretical structure and the engaging characteristics present a few limitations. These are discussed at the end of this review along with potential future research suggestions in order to improve the design procedures of mHealth services applied in adolescents with cancer, intending to optimize health-related behavior.

Key Words: *mobile health, adolescents, young adults, cancer, application design, engagement*

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Introduction

Adolescent cancer

Around 14,000 cases of cancer in teenagers and young adults are reported each year in Europe (1). According to the World Health Organization, (WHO) adolescence is defined between the ages of 10 to 19, acknowledging that this age range is flexible and depends on a variety of social, biological, socioeconomic, and gender factors(2). Adolescence is a unique stage that presents distinct developmental and psychological traits and marks the transition from childhood to adulthood (2). Accordingly, from the moment of diagnosis, throughout the treatment, and after recovery as cancer survivors, this population has specific care needs that require individualized support (1).

Many factors justify the differentiation of adolescents and young adults (AYAs) with cancer from other age groups, such as children and older adults (3). Firstly, the epidemiology of cancer in this population differs, as 10% of observed tumors are mainly pediatric, while 30% peak in adolescence. In particular, these rates include Hodgkin's lymphoma, Ewing's sarcoma, osteosarcoma, germ cell tumors and, more rarely, soft tissue sarcomas, with the remaining cases referring to early adult cancers (3-6). In fact, some types of cancer appear to occur frequently in adolescents with lower survival rates, compared to data found in the child and adult populations (6,7).

Mobile Health

Mobile Health (mHealth) is defined by W.H.O. as "the medical practice and public health practice supported by mobile devices such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices" (6). It incorporates the usage of mobile and wireless applications (e.g. SMS text messages, applications, mobile devices and the use of social media) aiming to provide health-related services (3). MHealth tools seem to have received broad recognition in recent years, especially in the children and adolescents population (7). Ramsey et al. (7) in their meta-analysis supported that a percentage as high as 95% of adolescents reported owning or accessing a mobile phone, 73% to a smartphone and 87% to a desktop or laptop (7). In addition, in recent studies it was estimated that 95% of 13-17 years old own or have access to a smartphone, which they often carry with them and use regularly to stay online (7).

It would be constructive to implement such applications into regular care of adolescents with cancer since they are often characterized as digital natives and are familiar with modern devices (6). Researchers indicate that children and adolescents seem to underestimate the traditional hand-written forms of interventions and are more willing to use mHealth devices while having more capabilities in learning their usage (8). Regardless of the fact that mHealth interventions seem to be a pole of attraction for AYAs, studies have supported that only 2% of them use a mHealth application usually (6). Despite the variety of existing applications and the expanded growth of mHealth interventions, only a quarter of them that have been downloaded are being used just once (4). Noteworthy, it has been estimated that populations from lower socioeconomic status have limited access to modern technology, using smartphones up to 25%, which could result in selection bias regarding the benefits of mHealth practices (5).

Achieving optimal success of mHealth interventions, characteristics such as staying connected and being familiar with modern technology seem to be inadequate (6). Especially in the field of chronic illnesses, the engagement of the patient in healthy behaviors, appears to be critical for disease prevention and the optimization of health conditions (9). It is noteworthy that this kind of intervention could reduce the effects of chronic stress and enhance resilience, self-management, and overall quality of life in patients undergoing cancer treatment (9). As a result, clinically developed and validated mHealth tools have the chance to become a personalized medicine tool in health care systems (9). In order to sustain long-term devotion to applications, creators should consider the implementation of engaging elements appealing to the user, such as ease of use, variety of contexts to avoid habituation as well as interactive elements in the early conceptualization of services (6,10-12). While the ultimate goal seems to be the adaptation of engagement strategies, there is little research on their development in mHealth services (12).

METHODS

The major objective of this review is to search the existing design theories incorporating engagement techniques that guided the creation of mHealth interventions applied in adolescents and young adults with cancer. Bibliographical research was conducted focusing on any kind of adolescent cancer and mHealth interventions in various databases. Specifically, most of the included articles come from Scopus, Pubmed, and one from W.H.O.. The present review includes both adolescents and young adults respecting the wide age range of this developmental stage.

RESULTS

The aforementioned research retrieved 40 articles, limited to the English language. The bibliographical research included specific theories that have broadly guided the creation of mHealth services aiming at user support and behavioral change. The present review focuses on Behavior Change Theory, User Centered Design, Social Marketing Theory, Social Cognitive Theory, Self-Determination Theory and Narrative Transportation Theory. The research indicates applied designing components based on theoretical frameworks that result in the successful engagement of mHealth interventions for adolescent cancer patients. In addition, it is supported that users have better possibilities to engage and cooperate with mHealth interventions when elements such as rewards, feedback, personalization, variation, convenience and gamification building design are integrated.

DISCUSSION

Theories

Behavior Change Theory

Researchers indicate that health promotion experts create health interventions, implementing behavior change theories in order to target groups (13). These theories appraise the norms, attitudes, and beliefs that may affect a person's health behavior (13). It is a fact that, although numerous theories exist, each one has a unique set of constructions and can differently affect behavioral modification (13). Studies focusing on the design building of mHealth applications show that optimal user engagement and thus behavior change can be achieved by positive reinforcement techniques such as rewarding the user for actively participating (9,12,14-20).

Persuasive technology (PT) is referring to interactive systems that are successful at encouraging various health and wellness-related behaviors by modifying and reinforcing the behavior and/or attitude (16). The model presents four categories of behavior change support features such as primary task support, dialogue support, credibility support, and social support features. (14,17,18). PSD features have an impact on behavior modification by helping the user accomplish the main goal, enabling human-computer interactions with feedback prompts, suggestions, or reminders while demonstrating the integrity of the system, and inspiring users by elevating social influence (16). The PSD model can be used to evaluate and create systems that affect attitudes and behaviors (16-18) .

According to Elena Vlahu-Gjorgievska et al. (16) concerning behavioral change, specific PSD features including categories can positively affect health-related behavioral changes. Researchers indicate that application designers should take into account the proper software design elements that will direct users toward the required attitude or behavior change aiming for effective management of patients' healthcare (16-18).

User-Centered Design

Studies present that User-Centered Design (UCD) is an interactive design method that involves users throughout the whole process of product creation (13). In order to optimize the usefulness of the final product, it is supported that a user-centered strategy which includes users in every stage, a multidisciplinary team, attentive and professional management, and identification of user's goals and objectives seem to be necessary (10). A requirements' analysis is the first step in the interactive cycles comprising in user-centered app design (6,12). In addition, UCD examines technology's acceptability, feasibility, and usability in the user's regular context (13). When implying this design technique, the designer should ensure that the user can utilize the finished product as intended while conveniently learning the usage (13). It is worth noting that nearly all applications have incorporated user feedback using the means of discussion and creation of interdisciplinary teams (10).

Studies indicate that the central idea of UCD is expanded by the procedure of cocreation (19,20). Cocreation design method enables the target audience of the finished product to make important decisions, incorporating users' voices in the application's design and content (20). The cocreation process can provide a user-friendly software that will be useful and pleasant for the intended patient audience (20). This enables young people who intend to use the application, to actively participate in the development of their own final product, sharing suggestions and experiences while also shifting the concentration from professional stakeholders to those who would actually use the finished product (19,20).

Social Marketing Theory

Social marketing applies classical marketing strategies to persuade people to engage in healthier activities (13,12). It is most effective when applied as a research-driven approach that incorporates end-user feedback in order to develop a customized campaign for a particular audience (13). When developing health campaigns, social marketing is essential since it reflects the audience's perspective

by integrating the "Four P's of Marketing" which include: product, pricing, place, and promotion (13).

Social Cognitive Theory, Self-determination Theory, Narrative Transportation Theory

Bernard et al. (21) argued that the theoretical structure which guided the development of the "Mila Blooms" application was based on social cognitive theory (SCT), self-determination theory (SDT), and narrative transportation theory (NTT). Specifically, increasing self-efficacy for adopting a healthy lifestyle throughout skill development, strengthening behavioral capacities, and enhancing social support are important components of SCT (21,22). On the other hand, SDT places a strong emphasis on the value of autonomy, relatedness (feeling valued by others), and competence in creating internal motivation for behavioral change (21,23). Finally, according to the narrative transportation theory, developing visual imagery for a narrative world and plot is crucial, and owing to this fact, persuasive messages can be more effectively received through a variety of cognitive processing mechanisms (21,24).

Implementations

As aforementioned, many different theories related to psychology, human-computer interaction, and marketing, point out various strategies, that could be included in mHealth interventions, in order to enhance the engagement of the user (12). Firstly, rewards is one of the most famous engaging strategies used, and could be separated into the promotion of both the extrinsic motivation such as getting a funny meme or gift cards, and the intrinsic motivation by the completion of a survey that could help another person (9,12,14,15,21,25-27). More specifically, based on social influence tactics and operant conditioning behavioral principles, it combines correspondingly rewards without special conditions or restrictions and desirable ones (12). What is more, adolescents seem to prefer mHealth tools that include colorful features, multimedia formats such as video and gif, variation of content and easy to use characteristics (2,11,15). For instance, apps that include a big number of steps in order to complete a function, maximize the complexity and minimize the convenience of usage, causing adolescent cancer patients displeasure (2). Novrianda et al.(10) concluded that especially the strategies of ease of use and perceived benefits are considered predicting factors of the actual usage of mHealth technology.

There are many more compelling capabilities that could increase the loyalty of the user to the mHealth interventions (15). Personalization is another very widely used engagement strategy that allows the operation of the system to the favorite preferences of the users, thus improving their satisfaction (2,11,15). More specifically in the field of adolescent cancer, this element offers the possibility of customizing the content (e.g. avatar or app environment), the tools, and the timing of intervention delivery according to the patient's will, enhancing his self-management skills (10,25). Moreover, reports of patients' symptoms in their own words is an implied example of tailored mHealth interventions designed to deliver personal health-related information that even younger populations could benefit from (8,25). Engagement is also boosted by developmentally and culturally acceptable content and graphics, as it focuses on the interests and the needs of targeted users (2,9,15). Another productive technique in mHealth services is the provision of feedback from the user on certain engagement content, for example by adding a thumbs up or thumbs down button (12,15). Lastly, time-appropriate interventions, such as text message delivery, via reinforcement learning algorithms and personalized sensing services seem to assist in long-term engagement (11,15).

Gamification, on the other hand, is a design process that incorporates many engaging strategies along with "gaming elements" like rewards, badges, avatars, and competitions, while also providing capabilities such as social integration, feedback on performance, and positive reinforcement (14,15,26-28). Clinically well-designed videogames for adolescents with cancer seem to promote intrinsic motivation as their content offers autonomous choices, chances for entertainment, shifting of attention, and user empowerment (21,27). "Positive addiction" caused by serious games seems to boost empowerment and resilience in cancer patients, resulting in higher levels of self-management (14,27,28). Heneghan et al.(6) in their research noted that the provision of positive feedback to stress-buffering neurotransmitters is the next stage in developing empowerment skills for patients (6). One extraordinary example of a serious mHealth game aiming atthe improvement of patients' perception ofchemotherapies, is the "Remission 2" (26). During this videogame cancer patients fight cancer cells using chemotherapy pills, antibiotics, and the body's natural defenses as bullets, resulting in increased positive emotions and self-efficacy (26).

Limitations and further research

The aforementioned theoretical frameworks and the engagement strategies present some worth-mentioning limitations (15). Firstly, it is supported that the majority of mHealth interventions available on the market are not based on a significant theoretical background, and experimental validation (14,15). The safety of consumers, might also be at risk due to the fact that some mHealth applications are not necessarily supported by scientific research (14). Additionally, the majority of the existing applications are lacking in evidence of sustained user engagement (14,15). Additionally, a gap between the scientific and commercial fields seems to exist, as applications that are offered to customers in online stores might not have a scientific base while the scientifically based ones are not accessible to them (15). Lastly, the cocreation design method is presented as a long-duration procedure with decreasing number of patients taking place in every stage (20).

Future research on mHealth design should emphasize appropriate methodological approaches and researches, in order to improve the available technological resources (15). More real-world clinical trial evidence is required and application descriptions ought to be accompanied by ratings of the functional quality and empirical backing (15). Furthermore, it is noted that the collaboration of scientists, software developers, and healthcare professionals is considered a key feature in the creation of high-quality, comprehensive, and commercially applicable mHealth tools for adolescents with cancer (15). In order to help other researchers understand the procedures used in the design of mHealth interventions, experts advise that researchers should give the public access to the development process of mHealth intervention (31).

Last but not least, it is supported that the evaluation of interventions includes qualitative techniques to investigate additional improvements, such as modifications in the technology platforms employed, in order to stay up-to-date with technological advancements (28).

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Review

Pregnancy eating habits and risk of tumor appearance in descendants in children and adolescents

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ABSTRACT

Proper nutrition is generally defined as a diet that includes all food groups in balanced amounts. The Mediterranean diet is considered to be the standard diet, which seems to equip the human body with the necessary elements to prevent diseases. The present review included 46 surveys conducted during the period from 1995-2005. Research shows that nutrition plays an important role in pregnancy, as inadequate or excessive food intake has been associated with long-term and non-communicable diseases in the offspring. This literature review focuses on the role the diet followed by women during pregnancy plays and especially on the data related to its association with the occurrence of cancer in the offspring. The data highlight the diet of pregnant women as a potential factor in the occurrence of various types of infant or childhood cancer. In particular, micro and macro elements, such as carotenoids, caffeine, folic acid, vitamin C seem to have effects on the fetus when consumed by pregnant women and are involved in epigenetic processes. In conclusion, the advantages and limitations of the various studies were identified, as well as points that need further research.

Key Words: *cancer, leukemia, pregnant, infant, nutrition*

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INTRODUCTION

A regular diet must include all food groups in balanced amounts, to be considered generally appropriate. Based on these data, the Mediterranean diet is considered as a balanced diet. According to its guidelines, the Mediterranean diet is characterized by a high intake of legumes, cereals, vegetables and fruits, high intake/ consumption of olive oil, low intake of saturated lipids, moderate intake of fish, low to moderate intake of dairy products (mainly in the form of dairy products) and low intake of meat and meat products. Therefore, the Mediterranean diet seems to meet all the criteria to be considered as a regular diet, both in terms of quantity and quality. The most important benefit of this diet is that it provides the necessary nourishing substances to pregnant women in order for the child has a reduced risk of developing diseases such as ALL (1).

From time to time, researchers have highlighted the correlation of the quantity of the pregnant woman's nutritional intake (insufficient/excessive nutrition) with long-term effects and occurrence of non-communicable diseases in children. Characteristically, a research conducted in 2017 by Luyckx et al. demonstrated that the development of a fetus in an obese intrauterine environment can permanently modify individual biological and metabolic pathways, resulting in adaptive pathophysiological alterations in the offspring and increased risks of non-communicable diseases in adulthood (2). The effect of the amount of nutritional intake of pregnant women was strengthened by other research data. The insufficient coverage of daily needs in vitamin C during pregnancy and the reduced ascorbic acid in the serum, appear to be associated with the risk of premature rupture of fetal membranes and premature birth (<37th week of gestation). In addition, the carbon metabolism cycle appears to be critical for the synthesis of DNA and RNA and the transfer of homocysteine to methionine and the formation of adenosylmethionine (SAM), which is the major methyl donor for DNA, RNA, proteins and lipids (3). In addition, folic acid and other B-complex vitamins have been proved to be important co-factors in pregnancy because it has been shown that they affect DNA methylation in children. In addition, maternal folic acid supplementation appears to protect against some childhood diseases, such as neural tube defects (4).

Childhood cancer, although rare, is a group of active and non-communicable diseases with a large number of unexplored data. Common types of cancer that occur in children include leukemia, neuroblastoma, lymphoma, Wilms's tumors, Hodgkin's disease, germ cell tumors, soft tissue sarcomas, retinoblastoma, and osteosarcoma. Leukemia appears to be the most commonly diagnosed childhood cancer, accounting for over 30% of all cases (5).According to a 2004 study, about 3,250 children under the age of 20 are diagnosed with leukemia each year, and about 2,400 cases are acute lymphoblastic leukemia (ALL) (6) - 80% of cases in children under 15 years of age appear to correspond to acute lymphoblastic leukemia (ALL), 17% to acute myelogenous leukemia (AML) and 3% to chronic myelogenous leukemia (6), (7). It is estimated that only 5-10% of cancers are due to a genetic mutation, while 90-95% appear to be due to lifestyle, infection and climate conditions. In this way, it is predicted that maternal diet is responsible for about 30-40% of cases (8), (9). A 2017 study in rodents confirmed that diet seems to have a greater impact on the development of cancer than the amount of carcinogen to which one is exposed, as food is made up of numerous substances and nutrients, each of which affects genes throughout the body and consequently many bodily functions (10). Initially, chromosomal shifts appear to be present at birth in children who later develop leukemia (11), (12), a factor that raises interest in the effect of prenatal exposure. Subsequently, birth weight has often been associated with an increased risk of ALL (13), especially in children <5 years of age (14), although zero results (15), (16) have been reported, which may indicate a quantitative or qualitative effect of mothers' nutrition during pregnancy (17). Dietary factors seem to be responsible for at least 30% of all types of cancer in developed countries (18). At this point, however, it would be important to note that most of the research that has been done, which mainly studied cases of leukemia, did not include cases of infantile leukemia, as the majority of these cases appear to have a specific genetic abnormality in chromosome zone 11q containing the MLL gene (19), (20).

MATERIAL AND METHOD

A variety of research data published worldwide from 2004 to 2017, in various countries, such as the USA and Greece, including meta-analyses and clinical studies, was studied in this literature review. . Many of the surveys included used the same or similar weighted questionnaires about food groups and were sometimes tailored to the needs/habits of each population and social group of participants.

So, a variety of food groups were studied and emphasis was placed on the results that represent the most commonly consumed food groups in the world.

Some food groups tested were fruits, vegetables, proteins, micronutrients from dietary sources and supplements (e.g. folic acid and vitamins), coffee and tea consumption (3), (4), (21). Foods were generally selected in the various surveys, representing a wide range of nutrients, including total calories, macronutrients, fiber, vitamins, minerals, antioxidants and micronutrients such as carotenoids and phytoestrogens. They also included processed meat products and vitamin supplements (multiple but also single vitamins) (6). The food groups, for example, surveyed in a 2005 study in Greece were cereals and starchy roots, sugars and syrups, legumes and nuts, vegetables, fruits, meat and meat products, fish and seafood, milk and dairy products and butter and margarine (22).

RESULTS

Research shows that pregnant women who follow a rich vegetable and fruit diet can help reduce the risk of childhood cancer. Research has shown that maternal intake of vegetables, fruits and protein sources is inversely related to childhood ALL. Consumption of carrots, beans or peas, melon and beef were the specific foods that were inversely associated with the disease. In a 2004 study by Jensen et al, in an analysis of the vegetable food group, the strongest inverse correlation of intake with ALL appeared for carrots and the fruit group. In the case of beef and legumes (which were considered non-expected elements), the antioxidant tripeptide glutathione, which is found in both meat and vegetable protein sources such as legumes, was considered to be a possible causal factor in this study and it was individually inversely associated with the disease. However, in this study, no correlation was found between consumption of broccoli, cauliflower, or Brussels sprouts and ALL risk. It has been shown, therefore, that increased maternal intake immediately before pregnancy (and, consequently, during it) of vegetables and fruits is associated with a reduced risk of ALL in offspring (6).

In a nationwide case study in Greece of children aged 12 to 59 months, it was found that the consumption of increased amounts of vegetables, fruits, fish and seafood by the mother during pregnancy is associated with a reduced risk of ALL in the offspring, while on the contrary increased consumption meat and meat products, sugars and syrups are associated with an increased risk of ALL in children. A marginal inverse correlation was also observed between maternal milk consumption and dairy products (22).

In a 2009 study by Kwan et al., six foods were found to be inversely related to the risk of ALL in children: carrots, melons, oranges, green beans, but also beans (fruit) and beef. This study, which had data from two phases (phase 1 and 2 from the NCCLS) found that the intake of vegetables, fruits, legumes and protein in the 12 months before pregnancy (and in conclusion and early pregnancy) is also related conversely with the risk of disease of the offspring. The results of this research generally agreed with those of the case study in Greece (Table 2). In contrast to research in Greece, however, the data here showed that the consumption of meat and meat products was associated with a moderate increase in the risk of disease (23).

In the case of processed meat, various research data seem to differ, with previous research showing, among other issues (with limited data at the time), a link between cold cuts as a potentially carcinogenic N-nitroso and childhood malignancies, including ALL (24) and subsequent research data to dispute the existence of this correlation regarding the occurrence of ALL (25), (26). In a 2004 study in the United States, the sausage team was extensively studied and it was found that the consumption of processed meat, hot dogs, sausages and bacon, lunches or whole meats by the mother were inversely associated with the disease, without statistically significant correlation. As the consumption of vitamins C and E has been shown by other studies to be able to inhibit nitration reactions and it has now been shown to prevent the formation of brain tumors in the offspring of pregnant animals fed N-nitroso precursors (27), Jensen et al., Examined in their research the interaction between the consumption of cold cuts and the intake of vitamins C and E (from diet and supplements). Consumption of these nutrients, however, did not appear to modify the risk of disease associated with the consumption of salted meat (6).

Subsequently, concerning caffeine consumption, it was found that there was an increased risk of developing ALL when mothers consumed more than four cups of coffee per day during pregnancy (28).

Caffeine consumption during pregnancy appears to be

associated with an increased risk of developing ALL, AML and the likelihood of an infant with leukemia, while others have failed to find a correlation, as summarized in a recent meta-analysis (28). However, there is some evidence from these studies that suggest that the increased risk of leukemia associated with maternal coffee consumption may be more pronounced in children born to non-smoking mothers (29).

Similarly, cola-based beverages have been associated with an increased risk of childhood ALL(30). It is worth noting that a general limitation of these studies is the lack of information on the type of beverages (eg caffeinated or not, green or black tea) that contain different nutrients and other compounds with anti-carcinogenic or precancerous properties (31)

On the micro-macro level, research has shown that exposure of the fetus to bioactive compounds (vitamins and minerals, fiber, peptides and amino acids) contained in vegetables, fruits and protein foods may contribute to reduce the risk of infant or childhood cancer (23). Fruits and vegetables contain vitamins and minerals that have been shown to have anti-cancer, anti-proliferative and anti-inflammatory effects. Their consumption reduces the occurrence of various types of cancer (Table 1).

Certain food groups, in particular, have been shown to reduce the risk of childhood leukemia. In fact, their consumption reduces more specifically the risk of developing infantile leukemia (32).

In particular, consumption of antioxidant micronutrients, such as provitamin A carotenoids, A carotene and B carotene, has been shown to be inversely related to the risk of ALL, as they may protect against oxidative damage to biomolecules such as lipids and DNA and therefore affect the risk of developing cancer. The prevention of DNA damage and the improved repair of DNA, in fact with supplements with fruits, juices and several carotenoids, has emerged from a wealth of research data (33), (34), (35), (36), (37). These data were also verified in a 2009 study, where maternal consumption of provitamin A carotenoids (found in fruits and vegetables) (AOR 50.77, 95% CI 0.60.0.98), and reduced glutathione consumption (found in protein contained in food) (AOR 50.49, 95% CI 0.27, 0.90) were inversely related to the risk of ALL (23).

Glutathione is an important physiological antioxidant that works in the synthesis and repair of DNA and plays a critical role in the detoxification of harmful compounds and the recycling of vitamins C and E in their reduced forms (6). The antioxidant glutathione tripeptide, found in both meat and vegetable protein sources such as legumes, appears to be individually inversely related to ALL (6), (23).

Vitamin intake and absorption during pregnancy appear to have a greater impact on the infant's vitamin reserves than on the mother's reserves (5). Vitamin B12 deficiency is one of the most common micronutrient deficiencies in pregnant women (38). Infants with B12 deficiency are then thought to be at risk of developing several neurological, hematological and developmental defects (39).

About iron and calcium, no specific association has been found with childhood cancer; however, studies highlight the importance of iron and calcium supplements to the pregnant woman to protect the mother herself (40). Research has also shown that catechins and quercetin (substances found in tea) are involved in leukemogenesis (22).

In addition, data from time to time have correlated fetal morphological development with fetal folic acid uptake and carbon metabolism (41), (42). In fact, daily folic acid supplementation of 400–800 lg is recommended for all women of childbearing potential, in order to reduce the risk of neural tube defects (NTD) in the offspring, from two months before to three months after conception (22). Maternal prevention of folic acid and other nutrients involved in carbon metabolism appears to affect the risk of childhood leukemia due to the importance of these nutrients to DNA (32). Folic acid, as a critical cofactor involved in DNA synthesis, is required for cell division and growth, thus explaining the use of antiplatelet drugs in cancer chemotherapy. This raises the question of whether taking folic acid supplements and therefore possibly the increased amount, could ultimately lead to increased risks of carcinogenesis (40). Descendants of women who took folic acid supplements (found naturally in many leafy vegetables) during pregnancy appeared to have a lower risk of ALL (43).

Finally, as for folic acid and Vitamin D, a study conducted in 2004 did not provide evidence of a significant reduction in the risk of ALL associated with maternal intake (through dietary supplements), before pregnancy, or with the consumption of any type. supplement, including those containing vitamin C (6).

In order to further investigate the above data, data were also sought on the dietary supplements received by the pregnant woman and their possible association

with the risk of cancer in the offspring. The nutritional status of the mother before pregnancy and the observance of nutritional supplements, along with the sex of the fetus, seem to be important factors that influence the way how supplements affect the outcome of the pregnancy and the survival success of the newborn (44).

Although the change in caloric and macronutrient requirements during pregnancy appears to be small, the need for micronutrients increases exponentially during pregnancy, especially for essential elements such as iron, folic acid, iodine, calcium and vitamin D (45). Previous studies have shown that maternal supplementation containing folic acid, with or without iron, and cod liver oil, containing vitamins A and D, is associated with a reduced risk of ALL in childhood (46). Nevertheless, in the studies, the regular use of any dietary supplement did not appear to be associated with disease risk (22), (23).

In a US study conducted in 2004, the food frequency questionnaires used included questions about the use of multiple vitamin supplements, multiple antioxidant supplements, and individual supplements containing vitamin A, B-carotene, vitamin C, zinc and selenium. Thus, the reception of each element was studied individually, as well as a multi-supplement. Consumption of individual micronutrients by supplements alone did not appear to be associated with ALL. The odds ratios were all close to 1.0 (ranging from 0.89 to 1.00) and none were statistically significant (6).

Discussion:

At this point, however, it would be important to pay particular attention to the limitations of the various studies which may have influenced the research data. An important issue that emerges is the recall bias, as most surveys use self-report questionnaires and therefore, there is an increased chance that a measurement error will occur, but also that nutritional factors are incorrectly correlated with each other by the participants in these surveys (23). Thus, care is required in the immediate attribution of risk or benefit to any particular food or nutrient. In addition, the sample size may be a limitation, especially for a heterogeneous disease, such as childhood ALL, which probably has a different etiology depending on the age of diagnosis (6).

Nevertheless, it is important to take into account the advantages of the studied publications. Most studies were performed on individually matched pairs of ALL cases of different ages that had been diagnosed over time and the questionnaires used covered a variety of food groups and micronutrients.

In addition, they covered socio-demographic variables and an extensive section assessing maternal nutritional intake, including standard portion sizes, during pregnancy, limiting the effect of confounding factors and often taking care of their weighting (28).

As further food for thought, a meta-analysis must be carried out - a systematic review of all foods and not only supplements, in the present possible studies, but also newer ones, in order to make full use of all possible data that could offer these surveys. It is also necessary to investigate further, as far as possible, infant cancer in relation to the mother's diet, as well as the possible association of a gene mutation with the pregnant woman's diet through possible DNA methylation, as the data in this sector seems to be deficient. In conclusion, it would be interesting to further investigate the inverse association of dietary glutathione with cancer risk observed in some studies (6).

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