Nutrition and Cancer

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Key Points

- Cancer is the second leading cause of death globally and is assumed to be a major global health concern.
- There is a multitude of studies about the influence of the different components of foods, diets, breastfeeding, fatness, and physical activity on mutagenic processes.
- Nutrition and cancer have a two-sided and complex association. Nutrition has been reported to increase the effectiveness of the immune system and to prevent cancer development or, conversely, promote malignancy.
- Cancer-protective foods such as whole grains, fruits, non-starchy vegetables, fish, and dairy products contain nutrients and non-nutrient bioactive components that are involved in the mechanisms

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for enhancing immunologic function, inducing apoptosis, enhancing antiproliferative function, donating electron to free radicals, activating carcinogen-metabolizer enzymes, as well as synthesizing retinoic acid.
- Those types of foods, with cancer-developing effects like red meat, processed and fast foods, alcohol, as well as sugar-sweetened beverages, exert carcinogenic effects mostly by causing obesity and overweight, unbalanced hormones, inflammation, oxidative stress, and lipid peroxidation.
- Cancer-preventing recommendations include keeping a healthy weight, having a physically active life, and following a diet rich in foods of plant sources and limited in red meat, fast foods, alcohol, and sugar-sweetened drinks.

Introduction

Cancer is caused by uncontrolled growth of cells which are able to invade other parts of the body [1, 2]. Symptoms of cancer depend on the location of the cancer. However, general symptoms of cancer include unintentional weight loss, excessive fatigue, fever, and skin changes [3].

Cancer is the second leading cause of death globally and is assumed to be a major global health concern. It is estimated that the number of affected people will reach 21.7 million by 2030 around the world [4]. In 2030, the global economic burden of cancer, including medical and nonmedical costs and income losses associated with work absences, is expected to be 458 billion USD [5].

There are many data showing that lifestyle and some nutrients are associated with cancer development as they are connected with other chronic disorders [6]. Epidemiological data from the past decade have demonstrated that a healthy diet can prevent up to 40% of all malignancies [7, 8]. Nevertheless, western lifestyle and its increasing trend in other places lead to decreased physical activity and fatness. In case of continuing current tendency, obesity and overweight have the potential to surpass smoking as the main risk factor for cancer.

The purpose of this chapter is to provide an overview of the effects of nutrition on the progress of cancer and its role as a part of therapeutic regimens.

Cancer Development

The malignant character of cancers results from a failure to preserve the balance between cell proliferation and apoptosis. Cancer mortality is caused by the uncontrolled growth of tumoral cells within body tissues and their subsequent damages [9]. The section below is a brief discussion of the cellular and molecular mechanisms associated with cancer.

Cellular and Molecular Mechanisms Associated with Cancer

Defects in DNA Repair

Deoxyribonucleic acid (DNA) is constantly influenced by environmental factors including ultraviolet (UV) radiation and cigarette toxic components and by harmful intracellular metabolites such as hydrogen peroxide and reactive oxygen species (ROS) that cause damage in DNA integrity and structure. Defects in cell ability to repair DNA damages such as DNA damage checkpoints and telomere repairs result in genomic instability [10]. Genomic instability leads to amplitude unfavorable mutations which can predispose a cell to become malignant [11]. The host physiological reactions to DNA damage are modulated by dietary elements, physical activity, and body fat content, which are discussed in the next sections.

Oncogenes

In a healthy condition, cell proliferation is regulated by a series of genes involved in cell-division cycle, programmed cell death (apoptosis), and survival signals like tissue growth factors and hormones as well as their receptors. Oncogenes are blemished genes that are

nonstandard versions of genes, which are normally responsible for cell proliferation. Oncogenes are the result of a set of mutations or epigenetic changes that progress the malignancy via the unbalanced proliferation of cells. Only a small group of all malignancies is associated with the inheritance of a cancer-linked germ-line mutation (5–10 percent of all cancers). In familial cancer cases, only one mutation contributes to developing cancer. The presence of these mutations does not ultimately lead to cancer but increase the risk of cancer development in relation to the general population. However, inherited mutations are a small proportion of cancer-risk factors, but the effect of other risk factors is the same as other people who have not inherited these mutations. For example, low physical activity increases the risk of breast cancer equally in both people with inherited BRCA1/2 mutation and people with no heritage of BRCA1/2 (7). Hence, identifying the people with these inherited genes is very vital to run preventive programs for the carriers and their family members.

Cancer Hallmarks

Phenotypic features of cancers are known as cancer hallmarks. In spite of the numerous pathways leading to genomic instability and its subsequent cancer development, the hallmarks of all cancers are relatively limited. Hallmarks of cancer include tumor-promoting inflammation, genomic instability and mutation, enabling replicative immortality, resisting cell death, activating invasion and metastasis, inducing angiogenesis, degranulation cellular energy, sustaining proliferative signaling, evading growth suppressors, and avoiding immune destruction. Genomic instability and Inflammation are two main characteristics, which enable other hallmarks to present.

Immune Response to Cancer

Malignant cells arise from body cells (self); however, they can induce immune responses. Indeed, products of oncogenes and mutated genes are dissimilar to usual cellular proteins; therefore, malignant cells elicit immune responses.

The theory of immune surveillance of cancer states that the host immune system detects and eliminates transformed cells before they grow into tumors and kills tumors after they formed.

Histopathologic findings show that tumors are surrounded by infiltration of mononuclear cells including T lymphocytes, natural killer (NK) cells, and macrophages. Furthermore, tumor-activated macrophages and lymphocytes are found in lymph nodes around the site of the tumor. Both innate and adaptive immunities are involved in tumor-fighting strategies.

CD8+ Cytotoxic T Lymphocytes (CTLs)

Peptides from tumor antigens are presented by class I histocompatibility molecules (MHC I). Only within a few minutes, the CTL transports granule proteins into the target cell, causing apoptotic death of the malignant cell.

Natural Killer (NK) Cells

One of the mechanisms where a tumor cell escapes the immune system is the loss of the MHC I to become undetectable by CTLs. Natural killer (NK) cells as innate immune cells destroy various types of tumor cells, mainly the transformed cells expressing lower MHC I on their surface.

Macrophages

Macrophages are another type of innate immune cells which, based on their activation state, play two contradictory roles, i.e., inhibiting and helping the development and spread of cancers. Typically, activated M1 macrophages are able to kill many tumor cells.

Antibodies

The role of antibodies against various tumor antigens has been demonstrated mostly in vitro. Data is lacking for the effectiveness of humoral immune responses against cancers.

Established Causes of Cancer

Factors known to alter the normal cellular processes and substantially lead to cancer include inherited mutations, steroid hormones, insulin and insulin-like growth factors, inflammation, and oxidative stress. Smoking, UV light radiation, alcohol drinking, and infections are among exogenous causes of cancers.

The Role of Nutrition in Cancer Development

A healthy immune system should detect and destroy the malignant cells. Breaking host immune surveillance leads to cancer progression. Cancer is more frequent in immunodeficient patients as their immune system is unable to defend against pathogens and cancer cells.

There is a multitude of studies about the influence of different components of foods, diets, breastfeeding, fatness, and physical activity on mutagenic processes. Nutrition and cancer have a two-sided and complex association. Food and nutrition have been reported to increase the effectiveness of the immune system and prevent cancer development or, conversely, promote malignancy.

Naturally, the immune system, to progress its defense mechanisms against pathogenic microorganisms and tumors, uses cytokines and reactive oxygen and nitrogen species that are toxic to target cells. Long-time production and elevated amounts of these materials cause chronic inflammation. Inflammation may trigger the promotion phase of carcinogenesis and increase the risk of malignancy.

Antioxidants as vitamins A and C, selenium, zinc, probiotics, and n-3 PUFAs as nutrition components enable the immune system to precisely target the infected or transformed cells and not damage the adjacent cells.

Whole Grains

The bran and germ of whole grains contain nutrients such as zinc, selenium, copper, and vitamin E. Furthermore, they have non-nutrient bioactive components including dietary fiber, phytoestrogens, and phenolic acid. Studies have shown anticancer effects of these components [12, 13]. For example, plasma levels of alkylresorcinols (a biomarker for whole-grain intake) are associated with a reduced risk of colorectal cancer [14]. Additionally, whole grains may bind to carcinogen components and reduce the risk of developing cancer.

Different mechanisms to mediate anticancer effects of dietary fiber have been suggested. Bowel microbial fermentation of fibers produces short-chain fatty acids, and their antiproliferative role for colon cancer cells is demonstrated [12, 15, 16]. Insulin resistance is one of the risk factors for colon cancer, and high amounts of fiber can lessen insulin resistance; therefore, fiber use leads to lower risk of colon cancer [17, 16]. Furthermore, fiber reduced the intestinal transit time and increased fecal bulk which helps to lower contact of colon epithelium with carcinogen agents of fecal bulk and subsequently reduced the risk of colon cancer [18].

In spite of cancer-preventing effects of whole grains, they are at risk of contamination with aflatoxin. Metabolites of this mycotoxin are genotoxic to cells and increase the risk of hepatocellular cancer [19–22]. Governments are responsible for controlling the safe storage of food in order to inhibit aflatoxin formation. In addition, people should be aware of aflatoxin hazard and avoid eating moldy grain and legumes.

Non-starchy Vegetables and Fruits

Non-starchy vegetables contain a number of anticancer components including fiber, vitamins, selenium, isothiocyanates, carotenoids, phenols, plant sterols, flavonoids, dithiolthiones, glucosinolates, indoles, limonene, and allium compounds. Many of these components are antioxidants that prevent exposure to ROS; for example, vitamins C and E donate an electron to free radicals in order to block their cellular damage [23–25]. It is probable that a combination of these components is responsible for reduced risk of cancer.

There are a series of studies suggesting molecular mechanisms for anticancer effects of carotenoids including beta-carotene, lycopene, and beta-cryptoxanthin [26–28]. They prevent some oncogenic mechanisms and inhibit cancer-cell development because of their role in the activation of carcinogen-metabolizer enzymes, the synthesis of retinoic acid [29, 30], enhancing immunologic function, inducing apoptosis; their

antiproliferative functions [31–33]; as well as their role as an antioxidant [34, 35].

Epidemiological studies found associations between consumption of vegetables and fruits and lower risk of several cancers involving mouth, pharynx, larynx [36], nasopharynx [37], esophagus [38], bladder [39], colorectum [40], and prostate cancers [41].

Citrus fruit includes multiple anticancer nutrients such as vitamin C, folate, flavonoids, and fiber. Consumption of citrus fruit has been associated with reduced risk of gastric cancer [24, 42].

There are data about the effect of fruits and vegetables on lung carcinoma and their mechanism of action. The results of these studies suggested that an increased uptake of fruits and vegetables is associated with a modest reduction in the risk of lung cancer. The findings were similar in the current smoker, past smoker, and never smoker groups [43]. Also, there are data about the role of carotenoids [44] and vitamin D [45] on lung cancer prevention.

Isoflavones (diadzein and genistein) have a similar structure to 17-beta estradiol and show elevated affinity to the estrogen receptor. Data from clinical trials and observational studies show that the use of exogenous estrogens increases the risk of lung cancers [46]. Estrogen receptors are present in both healthy and malignant lung tissues [47]. Estrogen has an inducing effect on non-small-cell lung cancer (NSCLC) [48].

The effects of vegetables in breast cancer are probably mediated through a hormone-dependent mechanism. Epidermal growth factor receptor (EGFR) is expressed frequently in estrogen-receptor-negative (ER-negative) breast cancer patients, and some vegetable constituents have been suggested to decrease the EGFR expression and reduce the risk of ER-negative breast cancer [49].

Red Meat

Prolonged and high-temperature grilling or barbecuing of meats leads to the production of heterocyclic amines and polycyclic aromatic hydrocarbons which have been shown in experimental studies to associate with a variety of cancers including colorectum [50], nasopharynx [51], lung [52], and pancreatic cancers [53]. Exposure to tobacco smoke is a principal risk factor for lung cancer. Components of tobacco smoke such as nitrosamines and polycyclic aromatic hydrocarbons are found in grilled meats [54, 55].

Using high-temperature cooking for red meats increases the production of glycation end products. Glycation end products appear to increase the risk of cancer [56].

Hem iron has an important role in oxygen transport, oxidative phosphorylation, DNA synthesis, and cell growth. Enhanced consumption of meat and its products in people who are not at risk of iron deficiency is likely to provide higher amounts of bioavailable iron. Higher amounts of iron are associated with the synthesis of ROS, cause DNA and cellular damage, and promote tumorigenesis [57]. Moreover, hem iron has been found to induce carcinogenic N-nitroso compounds [58]. These components are associated with cancer progression in animal models [59, 60].

Fish

Fish includes high concentrations of selenium and vitamin D, which have the potential to decrease the growth of cancer cells [61–63]. Furthermore, fish and mostly fatty fish include high amounts of long-chain omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids). Long-chain omega-3 fatty acids are associated with slower cancer cell growth by decreasing the production of inflammatory n-6 PUFA-derived eicosanoids [64, 65]. In addition, these fatty acids modulate the estrogen metabolism, signal transduction, and function of transcription factor [66]. It was found in an animal model study that omega-3 fatty acids through reducing inflammation and oxidative stress in the liver exert protective effects against hepatocellular carcinoma [67]. However, carcinogenic components of polycyclic aromatic hydrocarbons and heterocyclic amines can be found in grilled or barbecued fish [68], and there are some experimental data linking these chemicals to gastric cancer [69].

Dairy Products

Consumption of dairy products is inversely associated with the risk of colorectal and breast cancers [70, 71]. The antitumor effect of dairy products has been mostly attributed to their high calcium content. Calcium plays a significant role in cancer prevention through modulation of cell proliferation, differentiation, as well as apoptosis [72–74]. Intracellular concentrations of calcium are essential to cytotoxic T lymphocytes (CTL) and natural killer (NK) cells for killing cancer cells. On the other hand, proliferation and apoptosis of cancer cells are associated with the intracellular calcium content [75]. Also other components of dairy products including butyrate, conjugated linoleic acids, lactoferin, and vitamin D are linked to reduced risk of malignancy [76, 77]. However, there are some disagreements about the role of dietary intake or linoleic acid biomarkers in cancer prevention [78].

High consumption of dairy products is associated with increased risk of prostate cancer. Calcium, in high concentrations, has been found to inhibit the formation of 1,25(OH)2 vitamin D (active form of vitamin D). Therefore, it may lead to enhanced cellular proliferation in the prostate [79]. However, epidemiological studies did not find any relation between plasma levels of vitamin D and the risk of prostate cancer [79].

High intake of milk has been associated with increased serum levels of insulin-like growth factor-I (IGF-1) [80]. Increased circulating amounts of IGF-1 correlate with a higher risk of prostate cancer [81].

Alcoholic and Nonalcoholic Drinks

Alcohol is reported to increase the risk of a variety of cancers involving mouth [82], pharynx and larynx [83], esophagus [84], breast [85], stomach [86], lung [87], pancreas [88], liver [89], skin [90], kidney [91], and colorectum cancers [92].

The liver is responsible for alcohol (ethanol) metabolism, and alcohol can affect the liver's activity to metabolize nutrients, non-nutrient dietary component, as well as multiple hormones. Acetaldehyde is a toxic and carcinogenic metabolite of ethanol. Increased abuse of alcohol induces host cancer-developing mechanisms such as inflammation, oxidative stress, and lipid peroxidation [93]. Besides, it is hypothesized that alcohol acts as a solvent that increases the penetration of carcinogens such as tobacco components into cells, interrupts retinoid metabolism, and inhibits DNA repair mechanisms [94–96]. High consumption of alcohol is linked to malnutrition or poor dietary behaviors such as folate deficiency. This condition makes the host more prone to oncogenic effects of alcohol [97].

High and prolonged drinking of alcohol adversely affects the gut microbiome, which is associated with poor functioning of the gut barrier [98]. Thereby, the gut lumen will be exposed to higher levels of bacterial antigens such as lipopolysaccharide (LPS) and flagellin. Exposure to these bacterial products has been shown to enhance the risk of developing hepatocellular and colorectal cancers [99, 100]. For the explanation of the probable mechanism, it should be noted that conserved bacterial components such as LPS and flagellin can stimulate toll-like receptors (TLRs) and trigger inflammation, which is an important cancer-progressing mechanism.

Alcohol consumption is associated with increased levels of estrogen in the peripheral blood, whose role in the development of breast cancer is indisputable [101].

Additionally, alcohol may metabolize in mammary glands to acetaldehyde that its carcinogenic effect has been previously mentioned [102].

There are studies showing that drinking water contaminated with arsenic is associated with cancers of the urinary tract [103], skin [104], and lungs [105]. Arsenic and arsenic-derived metabolites facilitate cancer development through ROS causing disruption of the cell membrane and mitochondria, DNA damage, transcription factor dysfunction, and change in the expression of genes which are responsible for cell growth and survival [106, 107].

Tea contains abundant biologically active molecules such as polyphenols. There are animal model studies suggesting that green tea has a protective effect in bladder cancer development [108].

Coffee contains high levels of phenolic phytochemicals and natural diterpenes which exert

their anticancer effects via anti-oxidative and anti-inflammatory mechanisms, inhibition of DNA methylation [109], and induction of apoptosis [110, 111]. Coffee drinking has been reported to decrease the risk of cancers of the liver, mouth, pharynx, larynx, and skin (basal cell carcinoma and malignant melanoma) [112]. In addition, coffee is reported to decrease the risk of endometrium cancer. Consumption of coffee is linked to higher concentrations of sex hormone-binding globulin (SHBG) resulting in decreased bioavailable sex steroids in the blood [113–115]. Totally, a short luteal phase and low bioavailable sex steroids are associated with increased risk of endometrial cancer [113–116]. Coffee consumption is associated with low insulin levels [117]. Coffee can diminish the risk of developing endometrial cancer in an insulin-dependent manner. Adipose tissue secretes a number of biologically active molecules such as adiponectin. Coffee has been shown to increase circulating levels of adiponectin [114, 118]. High blood levels of adiponectin correlate with reduced risk of endometrial cancer [119, 120]. Adiponectin can induce apoptosis and exert anti-inflammatory and anti-angiogenic effects as well [118, 121].

Sugar-sweetened drinks, including sweetened waters, barley water, sodas, sports drinks, energy drinks, cordials, and tea- and coffee-based beverages, are increasingly consumed around the world. This can explain at least the partially increased prevalence of overweight and obesity and subsequently increased risk of cancer [122].

It is, thus, recommended to consume drinking water and unsweetened beverages and to not drink alcohol and sweetened drinks.

Fast Foods

Ease of access and acceptability of fast foods containing high amounts of fat, sugars, and starches are linked to universally elevated rates of overweight and obesity [123]. Consumption of processed meat and preserved vegetables is linked to elevated risk of cancers involving the stomach [124], pancreas [125], lung [126], esophagus [127], colorectum [128], and nasopharynx [51]. Preserved foods contain a high amount of salt. Animal studies have shown that salt can change the viscosity of mucus and augment the production of carcinogenic nitrosamines and N-nitroso chemicals [129]. Nitrosamines and their metabolites have been suggested to produce a cancer-developing effect [130]. Also, high salt consumption may result in colonization of *Helicobacter pylori*, which is the most significant risk factor for stomach cancer [131].

Like red meat, processed meats include high amounts of protein, hem iron, and fat which are underlying factors for cancer development [50]. Moreover, the fat content of processed meat is higher than in red meat, which results in higher secondary bile acids. Studies indicate the carcinogenic effect of secondary bile in gastrointestinal cancer [132].

In addition, processed meats such as sausages are exposed to high temperature during cooking procedure, which is associated with the higher production of heterocyclic amines and polycyclic aromatic hydrocarbons. Consumption of processed meats has been associated with increased insulin resistance and hyperinsulinemia which act as cancer-promoting factors [133].

Processed meats contain high amounts of exogenously derived N-nitroso compounds, nitrate, and nitrite, which have been implicated in tumorigenesis [134, 60].

Other Dietary Exposures

In general, it is believed that a weakened immune system and environmental toxins are responsible for cancer development [135]. Approximately 50% of cancer patients use some complementary and alternative medicine to strengthen their immune system and body detoxification from environmental pollution [136]. Therefore, a high proportion of cancer survivors follow a special anticancer diet or consume dietary supplements or both [137]. Cancer-fighting diet is recommended to patients with cancer. This includes raw vegetables and fruits, macrobiotics, alkaline diet, Gerson's regime, Budwig's regime, and low-carbohydrate or ketogenic diet. But there is yet no clinical evidence confirming the efficacy of such diet. Furthermore, there are data from clinical studies and case reports that reveal the harmfulness of such diet by increasing the risk of

malnutrition; weight loss; dehydration; metabolic acidosis; fatigue; sedation; anemia; deficiency in vitamins; calcium, iron, and zinc deficiency; hyponatremia; hyperkalemia; as well as hyperlipidemia [138].

Expert guidelines recommend patients with cancer to obtain nutrients from foods and to not consume supplements [139].

Nutritional insufficiency is endemic in many areas around the world, and supplementation is necessary to provide sufficient concentrations of nutrients in people with nutrient insufficiency.

Many clinical studies investigating the outcome of supplement intake in cancer survivors find no significant effect. However, some deleterious and advantageous effects are reported. For example, beta-carotene supplement is associated with increased risk of gastric and lung cancer, while vitamin E enhances mortality from colorectal and prostate cancers [140, 141]. However, both beta-carotene and vitamin E can decrease the toxicity of radiotherapy in patients with head and neck cancer while increasing the risk of cancer recurrence in smoker patients [142–145]. Selenium supplementation shows a dual function; its supplementation in selenium-deficient populations leads to reduced risk of stomach and lung cancer, while its consumption in persons with higher circulating levels of selenium increases the risk of these cancers [146]. Consumption of high-dose nutrition supplements is not recommended for cancer prevention.

In the absence of nutritional deficiency, people should achieve nutritional needs through diet alone. In addition, cancer clinicians should elucidate the potential adverse effects of supplements for cancer survivors, and in the case of necessity for supplementation, it should be supplied by a reliable source and personalized to the cancer patient by his/her physician.

Body Fatness

Experimental and epidemiological studies have shown that adult body fatness is associated with a higher risk of cancers affecting the head and neck [147], esophagus [148], liver [149], pancreas [150], colorectum [151], breast [152], kidney [153], stomach [154], gallbladder [155], endometrium [156], ovary [157], cervix [158], and prostate [159].

A number of underlying mechanisms are proposed for increased susceptibility to breast cancer in obese adults, which can also be extended to the other cancers.

Body fatness is associated with abnormal hormone profile, which plays an important role in carcinogenesis in their target sites. Obesity makes postmenopausal women more prone to invasive breast cancer. Increased risk of invasive breast cancer was evident among women with a BMI of more than 35 kg/m2 compared to women with a BMI of less than 25.0 kg/m2. In addition, mortality from breast cancer in women with grades 2 and 3 obesity was two times higher than that in nonobese women. Interestingly, normal body weight women who gained more than 5% of their body weight had increased risk of breast cancer compared to overweight or obese women who had no change in body weight [152]. During menopause, the breast tissue tends to have higher adipose content. After the decline of the production of estrogen from ovaries, breast tissue adipocytes are responsible for local estrogen production by conversion of androgens. Therefore, obese and overweight women have higher plasma concentration of estrogen that its role in the development of cancer is well-documented [160].

Additionally, obesity changes the adipocyte function in energy balance, whereby inflammation is increased and signaling of adipokine such as leptin and adiponectin [161] is changed. All these events are potential contributing factors to cancer [162, 163].

Obesity correlates with higher concentrations of circulating insulin, which, in turn, is associated with a greater risk of breast cancer [164]. Insulin by inhibiting the production of estrogen-binding protein makes estrogen more accessible for target tissues [165]. In addition, insulin can induce cancer development by supporting cell growth and preventing apoptosis [166, 167].

The common expectation is that fast body growth and breast tissue development in early life lead to DNA damage and cancer development. However, interestingly, obesity in early years shows a reverse association with the risk of breast

cancer in premenopausal and postmenopausal women. This association suggests a protective long-term effect of body fatness on the future risk of breast cancer. This association is controversial to the previously mentioned outcomes about the positive relationship between obesity and breast cancer risk in postmenopausal women. Abolished hormone profile in obese children and adolescents is responsible for reduced risk of cancer in adulthood.

Animal studies show that fat tissue-produced estrogen leads to earlier breast tissue development but also can reduce the susceptibility of breast tissue to carcinogenic agents [168]. Furthermore, young and obese girls are more prone to experience anovulation, linking to lower concentration of ovarian hormones and estradiol and diminished risk of breast cancer. Overweight and obese young people have lower blood concentration of IGF-1, which is the chief mediator of growth hormone [169]. Higher amounts of IGF-1 have been associated with increased risk of cancer [170]. Therefore, body fatness at a young age correlates to a reduced risk of cancer.

There are studies suggesting that greater body fatness may stimulate inflammation in the esophagus and thereby promote the progression of gastroesophageal reflux disease, which, in turn, may lead to the development of Barrett's esophagus. This condition may increase the risk of developing esophageal adenocarcinoma. Obesity is associated with increased risk of nonalcoholic fatty liver disease (NAFLD) that can adversely affect hepatic lipid metabolism. The severe form of NAFLD leads to oxidative stress and inflammation [171, 172], which are associated with liver cancer development.

Height and Birth Weight

Adult attained height is associated with increased risk of cancer involving the colorectum, prostate, lung [173], breast [174], endometrium [175], ovary [176], pancreas, kidney [177], and skin [178]. This might be due to the increased secretion of pituitary-derived growth hormone and insulin-like growth factors (IGFs) during the age of growth of taller people [179, 180]. Having more cells and increased number of cell divisions in taller individuals would result in increased risk of cancer development [181]. In addition, the increased length of the intestine in tall people seems to make them more exposed to mutagenic agents and therefore increased risk of colorectal cancer.

It is found that high birth weight is associated with increased risk of breast cancer [182] and malignant melanoma [183]. By an unknown mechanism, high birth weight pregnancies are linked to higher circulating levels of estriol and maybe increased activity of IGF-I [184, 185]. Also, additional measures at the birth time such as birth length, placental weight, and ponderal index are related to maternal blood levels of estrogen and breast cancer risk [184–189].

Physical Activity

Physical activity includes any work of skeletal muscles that consumes more energy than resting. Consequently, physical activity plays an important role in energy balance [139].

Physical activity influences a variety of immunologic, endocrine, and metabolic functions. Mostly, physical activity produces its anticancer effect through reducing body fatness. Body fat loss is associated with a reduction in plasma concentrations of estrogen, IGF-1, and fasting insulin as well as with insulin resistance and inflammation. The advantageous effect of physical activity on body fat reduction has been observed in cancers of the colorectum, breast, lung, liver, esophagus, and endometrium [164, 190–192].

Physically active persons revealed improvement in both the innate and adaptive immune responses and therefore in host tumor surveillance [193, 191]. Furthermore, physical activity is often linked to higher sunlight exposure and subsequently increased vitamin D absorption, which may prevent cancer development.

Lactation

Studies suggest a direct association between sex steroids and the risk of female malignancies such as breast, ovary, and endometrium cancers [194]. Lactation has been associated with lower risk of breast and ovarian cancers. The anticancer effect of breastfeeding is at least partially attributed to physiological amenorrhoea during pregnancy

and lactation, which suppress ovulation and thereby reduce host exposure to plasma estradiol [195–197].

The Role of Nutrition in Cancer Therapy

Research about nutrition and cancer is largely focused on investigating the effect of nutrients and dietary factors on cancer development. Many attempts have been made to design immune-enhancing diets for patients with cancer. Cytotoxicity during cancer chemotherapy can impair the nutritional status of patients and subsequently reduce the efficacy of antitumor treatments as well as lessen the quality of life in patients with cancer. In addition, there are studies that seek to establish standard immunonutrition for cancer patients who are undergoing surgery. Such a diet must be supplemented with high amounts of nutrients that can modulate immunological mechanisms such as glutamine; arginine; taurine; nucleotides; polyunsaturated fatty acids (omega-3); beta-carotene; vitamins A, E, and C; as well as trace elements including selenium and zinc, which support the host immune system to control inflammation and also stimulate protein synthesis [198–201].

Preoperative immunonutrition has been shown to correct the Th1/Th2 ratio in tumor-bearing and post-surgery states in patients with colorectal cancer [202]. Moreover, a randomized clinical trial on patients who had head and neck and esophageal cancer and received radiochemotherapy revealed that immunonutrition led to a sustained increase in the production of prostaglandin-E2, $CD4^+/CD8^+$ T-cells ratio and in the expression of CD3. Interestingly, immunonutrition is linked to increased expression of antioxidant enzymes, NADPH oxidase, as well as interleukin-6 receptor (IL-6r) and interleukin-10 receptor alpha (IL-10ra) [203]. Immunonutrition modulates immune cell responses affecting their phenotype. These alterations in the phenotype and abilities of immune cells make the host body capable of bearing oxidative stress and inflammation, which are caused by radiochemotherapy.

The efficacy of pre- and postoperative immunonutrition has been frequently studied in the surgeries of gastrointestinal tumors [204, 205, 198, 199]. Immunonutrition has been found to improve surgical outcome. In addition, it can be a cost-effective approach by reducing infectious complication and hospitalization days [206, 207]. It seems that preoperative use of immunonutrition is more efficient because its administration in the preoperation phase provides timely and adequate circulating levels of immunonutrients at the beginning of the postoperative phase, which then help in controlling inflammation [206]. However, the preoperative administration of immunonutrition has been shown to be less effective in malnourished patients with cancer [208].

Conclusions

There are many data indicating the substantial role of diet and nutritional ingredients in the prevention of cancer as well as their potential for application in therapeutic regimens for patients diagnosed with cancer.

It is clear that nutritional recommendations for cancer prevention require an evidence-based knowledge about causes of cancer and the nutritional behavior patterns of that population. It should be noted that our understanding of the context is largely based on animal and human studies, which are not comprehensive or systematic research works. However, there is increasing data linking nutrition and cancer can provide preventive and therapeutic approaches to diminish the risk of cancer and its related burden.

In 2018, the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) provided the general recommendations on cancer prevention and survival according to recent findings of diet, nutrition, and physical activity.

People with lower socioeconomic status are more likely to be exposed to cancer risk factors. Ministries' joint activities, public health administration, and public agencies are necessary to create an environment that is able to make people eager to consume a diet rich in whole grains,

non-starchy vegetables, and fruits. Additionally, it is essential that policymakers provide backgrounds to motivate the society to change their sedentary lifestyle and to limit consumption of fast foods, alcohol, and sugar-sweetened drinks as well as other processed foods high in fat, starches, or sugars. Governments are responsible for monitoring and controlling cancer risk factors especially those that people cannot necessarily affect them, for example contamination of drinking water by arsenic.

A broad set of policies is essential to support breastfeeding such as promoting breastfeeding in hospitals, offering free consultations in healthcare centers, workplace regulations, as well as marketing regulations of breast milk substitutes.

The recent advances in genetics, epigenetics, metabolomics, immunology, dietary metabolite biomarkers, as well as available data from systematic studies and computer analysis of intricate exposures lead to increase our knowledge about intricacies of the influence of nutrition on cancer. In spite of advances in the area of nutrition, immunity, and cancer, comprehensive studies are needed to exactly unravel the association between nutrients and immunological pathways contributing to cancer especially according to ethnic, age, sex, and environmental exposures such as smoking, UV light radiation, and infections. Future studies should investigate the optimal dose of pre- and postoperative immunonutrition to increase the efficacy of cancer surgery. These studies should evaluate the effectiveness of immunonutrition during neoadjuvant therapies as well.

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