

Nutrition and Cancer

Kenneth Lundstrom*

Pan Therapeutics, Switzerland

***Corresponding Author:** Kenneth Lundstrom, Pan Therapeutics, Rue des Remparts 4, Lutry, Switzerland.

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Abstract

The significant role of nutrition in relation to cancer has been documented already years ago. Progress in bioinformatics, genomics, proteomics, and nutrigenomics research has further confirmed the strong association of dietary intake and cancer for both prophylactic and therapeutic efficacy. Numerous studies have reported the association of dietary intake with the risk of various cancers such as breast, prostate, lung, ovarian, skin and stomach cancers, which has been confirmed by meta-analysis studies. Although additional large population clinical trials need to be conducted the trend is clear. Consumption of red meat and sugar-sweetened drinks may increase the risk of cancer, while vegetable and fruit intake seems to reduce the risk. Moreover, nutrition has been linked to changes in epigenetic mechanisms such as DNA methylation, histone modifications and RNA interference, providing evidence of the strong influence of nutrition on gene expression. Interventions in dietary intake and life style changes have demonstrated dramatic improvements in cancer patients. This review deals with the relationship between nutrition and various cancers, the effect of dietary intake on epigenetic mechanisms, the importance of nutritional interventions for prevention of disease, nutrition in cancer patients, and personalized nutrition.

Keywords: *Nutrigenomics; Epigenetics; Cancer Risk; Prevention; Therapy; Personalized Nutrition*

Abbreviations

15-HETE: 15-Hydroxyicosatetraenoic Acid; 25(OH)D: 25 Hydroxyvitamin D; APOE4-a: Apolipoprotein E4-a; BAL: Bronchoalveolar Lavage; CACS: Cancer Anorexia-Cachexia Syndrome; COX-2: cyclooxygenase-2; EAC: Esophageal Adenocarcinoma; ELISA: Enzyme-Linked Immunosorbent Assay; EPIC: European Prospective Investigation into Cancer and Nutrition; ESCC: Esophageal Squamous Cell Carcinoma; GAC: Gastric Cardia Adenocarcinoma; GNCA: Gastric Noncardia Adenocarcinoma; HEGU: Hexane/Ethanol Extract of *Glycyrrhiza uralensis*; ITCs: Isothiocyanates; miRNA: microRNA; NLCS: Netherlands Cohort Study; PMRP: Personalized Medicine Research Project; PGE2: Prostaglandin Eicosanoid; PGI2: Prostacyclin; PPAR: Peroxisome Proliferator Activated Receptor; PSA: Prostate Serum Antigen; PUFA: Polyunsaturated Fatty Acid; RNAi: RNA interference; SCID: Severe Combined Immune Deficiency; SNP: Single Nucleotide Polymorphism

Introduction

Statistics have indicated that cancer is still one of the most devastating and widespread diseases today [1]. However, cancer consists of a number of different diseases affecting more or less all organs and tissues, and development of cancer occurs through a multi-step process, which involves genetic and epigenetic changes over a long period of time [2]. Cancer is characterized by extensive heterogeneity both related to the type and aggressiveness of the disease. Although progress has been made for a number of cancers, there are still enormous unmet needs for cancer treatment. It has been extremely difficult to meet the ever increasing safety demands and costs for drug development and often only marginal improvement in drug efficiency has been obtained. For this reason, new approaches in drug discovery relying on recent progress in bioinformatics and the many areas of “omics” (genomics, proteomics and metabolomics) generating novel approaches have been welcome. Particularly improvement in sequencing technologies has provided access to a multitude of

data allowing studies on the effect of nutrition and bioactive food compounds on gene expression defined as nutrigenomics [3]. It has provided the means to investigate how nutrition may influence individuals with specific genetic features and also dietary input on epigenetic mechanisms.

The composition of the dietary intake has for decades been linked to disease development and prevention [4]. Related to cancer it was suggested already more than thirty years ago that nutrition was responsible for one third of cancers in the US [5]. Furthermore, The World Cancer Research Fund and American Institute of Cancer Research has concluded based on thousands of publications that dietary factors provide a significant worldwide contribution to cancer [6]. Another review on cancer prevention suggested that two-thirds of cancer-related deaths could be prevented by appropriate changes to dietary intake and lifestyle [7]. However, the nutritional effect on cancer complicates prevention and treatment due to differences in the types of cancer, the level of disease aggressiveness and the different stages of life at which cancer occurs. Moreover, individual variations such as the amount of food consumption, digestion and metabolism as well as geographical, ethnic and sociological diversity has made it more difficult to identify food components relevant to human health and prevention of disease [8,9]. This review deals with the effect of dietary intake on genetics and epigenetics, the prevention and therapy of nutritional interventions, and lifestyle changes on different types of cancers.

Genetics, Epigenetics and Nutrition

Genetic variations comprise of point mutations, resulting in single nucleotide polymorphisms (SNPs) [10], deletions [11], insertions [12] and copy number variations [13]. Furthermore, transposons can act as mutagens due to disruption or misplacement of functional genes [14]. On the other hand, epigenetic modifications are defined as heritable but reversible changes in gene expression without modifications in the primary DNA sequence [2]. DNA methylations represent epigenetic modifications where the mRNA transcription is reduced or terminated, but can also lead to up-regulation of gene expression [15]. For instance, hypermethylation of promoter regions can inactivate HIC1, INK4b and TIMP3 tumor suppressor gene expression [16]. Epigenetic changes relate to acetylation, methylation, ubiquitination and phosphorylation of histones H3 and H4 resulting in transcription activation or repression [17,18]. Finally, RNA interference (RNAi) provides down-regulation of gene expression through interference with mRNA by 21-23 nucleotide long single-stranded micro-RNAs (miRNAs) [19-21]. In a number of cases, nutrition presents an impact on epigenetic mechanisms. For instance, folate, polyphenols, selenium and retinoids influence DNA methylation and histone modification processes affecting cancer development and progress [22]. For example, bioactive compounds such as epigallocatechin gallate in green tea can alter DNA methyltransferase activity in esophageal, oral, skin, lung, breast and prostate cancer cells [23]. Studies confirmed inhibition of DNA methylation by epigallocatechin gallate in three out of four mouse models. Furthermore, a clinical trial in gastric carcinoma patients showed an association between decreased methylation of CDX2 and BMP-2 and increased intake of green tea. Nutritional modifications have also demonstrated an effect on reduction in aberrant miRNA expression and thereby decrease in cancer risk [24]. Moreover, more than 60% of human protein-coding genes are regulated by the more than 1800 miRNAs encoded in the human genome [25]. However, miRNAs might also be obtained from dietary sources such as plant foods and cow milk. Studies have indicated that miRNAs absorbed at nutritionally relevant quantities for food is sufficient to provide a biological effect. Furthermore, food components and dietary preferences influence serum miRNA profiles affecting biological processes thereby adding to the complexity of the crosstalk between nutrition and miRNAs in development of human disease. Generation of dietary miRNA databases have contributed to better understanding of physiologic and pathologic conditions also revealing the active regulation of several miRNAs in response to overnutrition and tissue inflammation.

Nutrition and Cancer

Bioactive food components such as proanthocyanidins, folate, flavonoids, isoflavones and catechins found in plants have been demonstrated to possess anti-carcinogenic activity through their anti-oxidant, apoptosis-inducing, immunomodulating and enzyme modulating properties (Table 1) [26]. A number of meta-analysis strongly supports the preventive and therapeutic benefits of dietary changes in relation to various cancers [27,28] as described below and summarized in Table 2. Due to the vast number of studies and findings supporting nutritional influence on more or less all forms of cancers, it is necessary to focus on examples from certain cancer indications here.

Table 1: Bioactive compounds and their sources.

Bioactive compound	Source
Vitamin A	liver, milk, cheese, fish
B1	whole grains, dried beans, liver, nuts, seeds
B2	soybeans, meat, eggs, mushrooms, milk, cheese, yogurt
B3	mushrooms, peanut butter, meat, whole grains
B6	potato, banana, oatmeal, meat, fish, chickpeas, lentils, pistachios
B7 (biotin)	sweet potatoes, nonfat milk, yogurt, peanuts, almonds, eggs, soy protein
B9 (folate)	asparagus, spinach, lettuce, Brussels sprouts, beets, broccoli, corn, peas, oranges, bread, enriched pasta, wheat germ, liver, chickpeas, lentils
B12	milk, cheese, yogurt, soy and rice beverages, meat, fish, eggs
C	citrus fruits, oranges, grapefruit, kiwi, strawberries, mangoes, papaya, peppers, broccoli, Brussels sprout, tomatoes, leafy vegetables
D	milk, soy and rice beverages, fish, eggs, meat, fish liver oil
E	vegetable oils, avocados, leafy vegetables, wheat germ, nuts, peanut butter
K	broccoli, soybeans, kale, collards, beets, spinach
Carotenoids	cantaloupe, pink grapefruit, broccoli, leafy vegetables, carrots, sweet potatoes
PUFAs	walnuts, sunflower seeds, flax seeds and oil, corn oil, soybean oil, safflower oil, fish (salmon, mackerel, herring, tuna, trout)
Proanthocyanidins	grapes, apples, unsweetened chocolate, red wine, blueberries, cranberries, black currents, hazelnuts, pecans, pistachios
Polyphenols	cloves, star anise, cocoa powder, Mexican oregano, celery seed, dark chocolate
Flavonoids	onions, parsley, blueberries, black tea, green tea, oolong tea, banana, citrus fruits, <i>Ginkgo biloba</i> , red wine, dark chocolate
Isoflavones	soybeans
Isothiocyanates	broccoli, Brussels sprout, cabbage, cauliflower, kale, mustard, radish

PUFAs: Polyunsaturated Fatty Acids

Table 2: Examples of associations between nutrition and cancer.

Cancer type	Nutrient/Source	Effect	Ref
Breast	Meta-analysis on fiber intake	Inverse dose-dependent association between cancer risk and fiber intake	[27]
	Dairy food, soy isoflavone	Reduced cancer risk	[28,31]
	Vitamin D	Cancer protection of vitamin D	[33]
	PUFAs	Cancer prevention	[34]
	Sugar-sweetened drinks, red meat	Increase cancer risk	[36]
	Vegetables, fruit, flavonoids, isoflavones	Reduced cancer risk	[36,53]
	Eggs	Moderately increased cancer risk	[58]
Brain	Spices	Cancer prevention and treatment	[69]
	Red meat	Association with glioma risk	[38]
	PUFAs in fish	Reduced brain tumor risk	[39]
Prostate	Ast, Dau, Pec isolated from plants	Neuroprotection in neuroblastoma cells	[40]
	Green tea	Reduced tumor size in SCID mice	[41]
	Green tea/EGCG	Reduced cancer risk in Chinese men	[42]
	Leaf juice from <i>C. papaya</i>	Tumor inhibition in cancer cells	[43]
	Astaxanthin	Inhibition of tumor growth in nude mice	[44]
	Nigerian fruits, herbs, spices	Prevention of prostate cancer	[45]
	Eggs	Potential cancer risk	[58]
Lung	Spices	Cancer prevention and treatment	[69]
	Cruciferous vegetables	Inverse association between vegetable intake and cancer risk in non-smokers	[47]
	Vitamin E	Protection against lung cancer	[48]
	Grape seed procyanidin extract	Anti-proliferative activity	[49]
	Licorice extract	Apoptosis, reduced pulmonary metastasis	[50]
	Red meat	Weak association with overall mortality	[51]
	Flavonoids	Reduced cancer risk	[53]
Ovarian	Spices	Cancer prevention and treatment	[69]
	Acrylamide	Association between acrylamide intake and genes for ovarian cancer risk	[52]
	Isoflavones	Reduced cancer risk	[53]
	Quercetin	Anti-cancer activity in animal models	[54]
	Dietary carbohydrates	Increased ovarian cancer risk	[56]
Skin	Eggs	Potential cancer risk	[58]
	Folate	Potential cancer prevention	[60]
	Vitamin D	Reduced mortality	[61]
	Epicatechins, proanthocyanidins	Epigenetic chemoprevention	[63]
	Proanthocyanidins	Inhibition of skin cancer growth	[59]
Colorectal Stomach	Caffeine, coffee	Reduced melanoma risk	[64]
	Flavonoids, isoflavones	Reduced risk of colorectal cancer	[53]
	Fruits, vegetables	Reduced risk of colon cancer	[67]
	Fruits, vegetables	Reduced risk of EAC, ESCC, GCA	[68]
Pancreatic	Spices	Cancer prevention and treatment	[69]
	Vegetables, fruits	Reduced cancer risk	[70,71]
	Carotenoids, tocopherols	Reduced cancer risk	[72]

Ast: Astragalin; Dau: Daucosterol; EAC: Esophageal Adenocarcinoma; EGCG: Epigallocatechin Gallate; ESCC: Esophageal Squamous Cell Carcinoma; GAC: Gastric Cardia Adenocarcinoma; Pec: Pectorinalin; Pufas: Polyunsaturated Fatty Acids; SCID: Severe Combined Immune Deficiency

Breast Cancer

Several studies have indicated that fiber intake may reduce the risk of breast cancer [29,30]. However, as some results have been inconclusive, a meta-analysis of ten cohort studies including 712,195 patients was carried out [27]. Geographical regions, length of follow-up or menopausal status of individuals showed no association between dietary food intake and breast cancer risk, but a significant inverse dose-response link between fiber consumption and risk of breast cancer was observed. Another meta-analysis study with more than one million participants suggested that increased consumption of total dairy food, excluding milk, may be associated with a reduced breast cancer risk [28]. Furthermore, a meta-analysis study of 4 trials on breast cancer reoccurrence and 14 studies on breast cancer incidence indicated that soy isoflavone intake from soybeans is associated with a significantly reduced breast cancer risk in Asian populations [31]. The same association was not found in Western populations. Furthermore, the link between olive oil intake and breast cancer risk in postmenopausal women was investigated in 62,284 women in the Mediterranean, which indicated that there was no association between olive oil intake and the risk of estrogen or progesterone receptor-positive tumors [32].

The effect of vitamin D on breast cancer risk was evaluated in women in Iran, commonly known for high prevalence of vitamin D deficiency [33]. The study was based on food frequency questionnaires and measurement of serum 25-hydroxyvitamin D (25(OH)D) in blood by an ELISA method. Women in the fourth quartile of serum 25(OH)D level showed 3 times lower risk of developing breast cancer than those in the first quartile supporting the protective effect of vitamin D. Furthermore, it was demonstrated that not the total vitamin D, but the dietary intake was associated with decreased cancer risk.

Important recognized factors influencing the risk of breast cancer comprise of diet and exercise. For instance, n-3 polyunsaturated fatty acids (PUFAs) play a crucial role in breast cancer prevention [34]. Moreover, exercise has been shown to affect chronic prevention of cancer. The synergistic effect of n-3 PUFA intake and exercise in breast cancer prevention has now been outlined for future research strategies [34]. Interestingly, one fourth of breast cancer cases have been attributed to inappropriate lifestyle choices and obesity or overweight, which triggered a 6 month pilot study on dietary and lifestyle interventions [35]. Overweight and obese women at high risk of breast cancer received coaching on cognitive-behavioral therapy and dietary modifications, which resulted in improved metabolic and inflammatory profiles in these individuals. In another study, the association between adolescent and early adulthood inflammatory dietary patterns with breast cancer was monitored among 45,204 women [36]. During a 22 year follow-up study 1,477 women were diagnosed with breast cancer in which an adolescent and early adulthood dietary pattern characterized by inflammation was associated with an increase in incidences of premenopausal, but not postmenopausal breast cancer. Overall, a diet characterized by high intake of sugar-sweetened and diet soft drinks, refined grains, red and processed meat and margarine and low intake of green leafy vegetables, cruciferous vegetables, and coffee may enhance the incidence of premenopausal breast cancer. Similarly, women consuming a modern diet consisting of more grains, dairy and sugar products and less fruit, vegetables and poultry demonstrated lower tissue omega-3 fatty acids and higher omega-6 and trans fatty acids, which is associated with estrogen-receptor negative breast cancer risk [37].

Brain Cancer

The impact of nutrition on the risk of brain cancer has also been investigated. In this context, some inconsistency related to the association between red meat consumption and gliomas triggered a systematic review and meta-analysis on 18 published studies on unprocessed red meat, processed meat and total red meat consumption in relation to gliomas in adults [38]. A positive significant association was found between intake of unprocessed red meat and risk of glioma. However, consumption of processed meat was not related to increased glioma risk. Furthermore, total red meat intake was not linked to risk of glioma in case-control and cohort studies. It has also been postulated that fish rich in ω -3 polyunsaturated fatty acids is associated with a lower risk of several types of cancer and beneficial for brain development. To evaluate the possible link between fish intake and brain tumor risk, a meta-analysis comprising 9 observational studies was conducted [39]. The results suggested that fish consumption might contribute to a lower brain cancer risk, but further cohort studies needs to be conducted to confirm these findings.

On a more basic research level, neuroprotective effects were evaluated for daucosterol (Dau), pectolinarin (Pec) and astragaloside (Ast), isolated from the edible plants *Cirsium setidens* and *Aster scaber*, in human neuroblastoma cells [40]. Ethyl acetate fractions of *C. setidens* and *A. scaber* provided neuroprotection in SK-N-SH neuroblastoma cells by down-regulation of MAPK pathways, associated with cancer development, and up-regulation of the HO-1, CAT and SOD2 anti-oxidant genes.

Prostate Cancer

The anti-cancer properties of green tea extracts, providing inhibition of oxidative stress and angiogenesis, were explored in human LAPC4 prostate tumor bearing severe combined immunodeficiency (SCID) mice by replacing their drinking water with brewed green tea [41]. A significant decrease in tumor volume and tumor size was observed to correlate with green tea polyphenol contents in tumor tissue. The anti-carcinogenic effect of polyphenol epigallocatechin gallate found in green tea was evaluated for prostate cancer risk in Chinese men in Hong Kong habitually consuming green tea [42]. A comparison of 440 prostate cancer cases with 395 controls indicated that the cancer risk was inversely associated with green tea consumption and intake of polyphenol epigallocatechin gallate. However, these results need to be confirmed in larger studies. In another approach, leaf juice and various extracts of the tropical plant *Carica papaya* were subjected to an anti-proliferative and anti-metastatic activity study in cell lines representing benign hyperplasia, tumorigenic and normal cells of prostate origin [43]. Potent growth inhibitory and cytotoxic activities were obtained for all prostate cells except for normal RWPE-1 and WOMY-1 cells.

It has also been demonstrated that the dietary carotenoid astaxanthin affects tumor proliferation, apoptosis, and miRNA overexpression in an animal model [44]. Nude mice subcutaneously inoculated with androgen-independent prostate cancer PC-3 xenografts were intragastrically administered 100 mg/kg astaxanthin, which significantly inhibited tumor growth in comparison to olive oil intake. Moreover, astaxanthin treatment resulted in enhanced levels of tumor suppressor miR-375 and miR-487b in tumor tissue. In another study, the association of Nigerian food and prevention of prostate cancer was evaluated [45]. Local plants such as African bush pear or plum (*Dacryodes edulis*), horseradish tree (*Moringa oleifera*), and clove (*Syzygium aromaticum*) provide fruits, herbs and spices as food ingredients containing polyphenols (ellagic acid, gallate, methylgallate, kaempferol, and quercetin). Furthermore, the Nigerian diet contains soy beans (isoflavones), chili pepper (capsaicin), and green tea (epicatechin). As prostate cancer is highly prevalent in Africa a diet rich in fruits and vegetables may dramatically reduce the cancer risk and delay the onset of disease. Moreover, specific nutrients and food ingredients such as folate (vitamin B9), vitamin B12, selenium, zinc, and phytochemicals (sulforaphane, polyphenols, curcumin, and allyl sulfur compounds) have demonstrated strong influence on epigenetic mechanisms and although their precise actions are complicated to determine due to pleiotropic effects, they might be targets for chemoprevention of prostate cancer [46].

Lung Cancer

Related to lung cancer, 82,330 participants with no previous history in lung cancer were subjected to a study on the association of cruciferous vegetables, a rich source of isothiocyanates, with cancer risk in Japan [47]. After a 14.9 year follow-up, a total of 1499 individuals were diagnosed with lung cancer. A non-significant inverse trend between vegetable intake and lung cancer risk in men was observed. Analysis by smoking revealed that a significant inverse association between vegetable consumption and lung cancer risk could be established in non-smokers. In another approach, the association of vitamin E intake and lung cancer risk was evaluated in a meta-analysis study covering relevant publications between 1995 and 2015 [48]. The study indicated that with every 2 mg/d increase in dietary vitamin E intake, the risk of lung cancer decreased statistically by 5%, suggesting a protective effect for vitamin E.

The anti-proliferative and proapoptotic effects of grape seed procyanidin extracts acting by inhibition of cyclooxygenase-2 (COX-2)/prostaglandin eicosanoid (PGE₂) pathways and also affecting the metabolic pathways of prostacyclin (PGI₂) and 15-hydroxyicosatetraenoic acid (15-HETE) were investigated in human lung premalignant and malignant cells and in human bronchoalveolar lavage (BAL) cells *ex vivo* [49]. Furthermore, the bioactivity of oral administration of leucoselect phytosome, a standardized grape seed procyanidin extract, was analyzed in lungs of individuals participating in a lung cancer chemoprevention trial. The treatment significantly increased PGI₂ and

15-HETE production. Culture supernatants from baseline BAL cells treated *ex vivo* with grape seed procyanidin extracts significantly reduced proliferation of lung premalignant and malignant cells. Also, licorice extracts containing glycyrrhizin have demonstrated anti-carcinogenic activity [50]. However, due to hypokalemia and hypertension induced by glycyrrhizin, a hexane/ethanol extract of *Glycyrrhiza uralensis* (HEGU) lacking glycyrrhizin but containing the active compound licoricidin was prepared. HEGU induced apoptosis and G1 cell cycle arrest in DU145 human prostate cancer cells and licoricidin inhibited metastasis in the 4T1 mammary cancer model. Furthermore, treatment with HEGU and licoricidin reduced pulmonary metastasis.

In a population-based case-control study the association of processed red meat consumption on all-cause mortality among patients with cancers of the upper aerodigestive tract (UADT) and lung was conducted after 12 years of follow-up using a diet history questionnaire [51]. The outcome was a dose-response trend and a weak association between red meat consumption and overall mortality among lung cancer cases.

Ovarian Cancer

In the case of ovarian cancer, several studies have been conducted to evaluate a potential link between nutrition and risk of cancer. For instance, epidemiological studies have suggested a positive association between dietary acrylamide intake and ovarian cancer, which have recently been expanded to analysis of gene-acrylamide interactions [52]. The prospective Netherlands Cohort Study (NLCS) included 62,573 women of which a random subcohort of 2589 women was sampled for a food frequency questionnaire. Among a total of 57 SNPs and 2 gene deletions, no statistically significant interaction was found between dietary acrylamide intake and gene variants. However, several nominally statistically significant interactions occurred between dietary acrylamide intake and SNPs in the HSD3B1/B2 gene cluster. These results suggested that acrylamide may cause ovarian cancer through action on sex hormones, which however needs to be confirmed in additional studies. In another study, the association between dietary flavonoid and lignan intake and risk of various cancers (lung, stomach, breast, and ovarian) was evaluated in a meta-analysis of 143 studies [53]. The study revealed an association of flavonoids with breast, colorectal, and lung cancers and isoflavones with ovarian breast, and colorectal cancers. Another meta-analysis on the flavonoid quercetin contained 220 publications including prospective and case-control studies [54]. Despite previous findings in laboratory settings of protective effect of quercetin, based on inhibition of tumor cell growth, apoptosis, and angiogenesis in human and animal cell lines as well as in animal models, no significant decrease in ovarian cancer could be established. For this reason, additional studies are needed. The traditional herbal medicine Evodiamine from *Evodia rutaecarpa* has been described to possess anti-cancer activity. The viability of human ovarian cancer cell lines A2780, A2780CP, ES-2, and SKOV-3 was inhibited by Evodiamine, which could be reversed by addition of caspase inhibitors VAD and DEVD [55]. Furthermore, the JNK inhibitors SP600125 and JNK1, but not other MAPK or AKT inhibitors prevented the apoptotic activity of Evodiamine.

The association between carbohydrate intake, glycaemic load, and glycaemic index and risk of ovarian cancer was investigated in African-American women (406 ovary cancer cases and 609 controls) [56]. The study revealed an inverse association between fiber intake and ovarian cancer risk. Higher glycaemic load was positively linked with the risk of ovary cancer. No associations were discovered for starch and glycaemic index. The study also indicated that high intake of total sugars and glycaemic load were associated with a higher risk for ovarian cancer. In another study, the association between dietary intake of 28 foods/food groups and 29 nutrients with epithelial ovarian cancer risk was estimated by using dietary questionnaires in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [57]. Four foods/nutrients, which showed statistically significant association with ovarian cancer risk, were selected for evaluation on the NLCS. None of these 4 selected dietary factors (cholesterol, polyunsaturated and saturated fat, and bananas) showed a significant link to ovarian cancer risk. However, a meta-analysis of the EPIC and NLCS indicated a higher risk of ovarian cancer for high intake of saturated fat.

A meta-analysis was conducted to summarize the dose-response relationship between egg consumption and the risk of breast, prostate and gynecological cancers [58]. The linear dose-response meta-analysis showed a non-significantly increased risk of breast cancer, but consumption of more than 5 eggs per week was significantly associated with an increase in cancer risk compared to no egg consumption.

tion. Similar results were obtained for ovarian cancer and fatal prostate cancer. Overall, high egg consumption may be associated with modestly elevated breast cancer and the association between egg consumption and ovarian and prostate cancers cannot be ruled out.

Skin Cancer

The increase in exposure to UV light has dramatically enhanced the occurrence of skin cancer and it has been claimed that the incidence of skin cancer is equivalent to the incidence of malignancies in all other organs combined [59]. Folate has been recognized as a cancer prevention agent providing precursors for DNA repair and replication mechanisms and generating methyl groups necessary for gene expression control [60]. Inefficient delivery of micronutrients to the skin and photolysis of folate has contributed to folate deficiency. Supplementary folate intake may provide a critical role and effective topical delivery might be a relevant strategy for cancer prevention. Another study targeted the effect of vitamin D intake related to reduction in mortality rates of cancer and cardiovascular disease [61]. Doubling of the vitamin D levels generated a reduction in all-cause mortality rates of 7.6% for African females and 17.3% for European females while the reduction was 0.6% lower in average for men. The increase in 25(OH) D levels in serum is the most cost-effective approach to reduce global mortality rates due to the low cost and few adverse effects of vitamin D. Alternatively, moderate UVB irradiation can be applied. The anti-carcinogenic and anti-melanoma effects of vitamin D3 has been hampered by defects in vitamin D signaling due to D3 activation/inactivation and vitamin D receptor (VDR) expression, which considerably affects melanoma progression [62]. Furthermore, D3 comprise of multiple bioactive forms interacting with alternative receptors, which complicated treatment of melanoma.

The bioactive dietary components epicatechins (green tea) and proanthocyanidins (grape seeds) have demonstrated chemoprevention of UV-induced skin cancer [63]. The epigenetic mechanism is based on UV-induced DNA hypermethylation and histone modifications in the skin resulting in silencing of Cip1/p21 and p16 INK4a tumor suppressor genes. The contribution of phytochemicals such as grape seed proanthocyanidins has demonstrated significant inhibition of UV radiation-induced skin tumor development and malignant transformation of papillomas to carcinoma in animal models [59]. A grape seed proanthocyanidin-supplemented diet provided inhibition of skin tumor growth through inhibition of inflammation, rapid repair of damaged DNA and stimulation of the immune system. Interestingly, caffeine has been indicated to possess the potential of preventing UV radiation-induced carcinogenesis and inhibition of growth of melanoma cells [64]. Data from three large cohort studies of more than 200,000 individuals evaluated the association of coffee consumption and melanoma risk. The higher total caffeine intake associated with a lower risk of melanoma was more apparent in women than in men. Moreover, decaffeinated coffee showed no association with a reduced risk of melanoma.

Colorectal and Stomach Cancer

In the context of gastric and esophageal cancers diets rich in vegetables and fruits were evaluated in the EPIC study [65]. The result demonstrated a statistically significant inverse association between nutrition and the risk of esophageal squamous cell carcinoma. The association was independent from the quantity and variety of fruits and vegetables consumed. The main active ingredients catechins and theanine of green tea have been linked to some health benefits related to various cancers such as stomach, esophageal, colon and ovarian cancers [66]. The risk of colon and rectal cancer was evaluated in a case-control study in Western Australia related to fruit and vegetable consumption [67]. The results showed no association between fruit and vegetable intake and risk of proximal colon cancer. In contrast, Brassica vegetable consumption demonstrated an inverse association with proximal colon cancer. In the case of distal colon cancer, significant negative trends were observed for total fruit and vegetable intake. Intake of dark yellow vegetables and apples showed a significantly decreased distant colon cancer risk. However, an increased risk for colorectal cancer was associated with fruit juice intake. Another study targeted fruit and vegetable intake in relation to the risk of esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), gastric cardia adenocarcinoma (GCA), and gastric noncardia adenocarcinoma (GNCA) [68]. The Dutch NLCS study showed a significant inverse association between intake of raw vegetables and the risk of EAC. Similarly, Brassica vegetable intake was associated with the risk of GCA and citrus fruit consumption was inversely linked to EAC and GCA. Furthermore, vegetable and fruit intake was inversely associated with the risk of ESCC and EAC in smokers.

Spices have been used as traditional medicines providing anti-oxidant, anti-inflammatory and immunomodulatory effects in various cancers such as lung, liver, breast, stomach, colorectal, cervix and prostate cancers [69]. In this context, *Curcuma longa* (turmeric), *Nigella sativa* (black cumin), *Zingiber officinale* (ginger), *Allium sativum* (garlic), *Crocus sativus* (saffron), *Piper nigrum* (black pepper) and *Capsicum annum* (chili pepper) have been utilized. They contain several important bioactive compounds such as curcumin, thymoquinone, piperine and capsaicin. Spices can act by induction of apoptosis, inhibition of proliferation, migration and invasion of tumors, and sensitization of tumors to radio- and chemotherapy.

Pancreatic Cancer

Being the fourth most common cause of cancer-death with a depressing average five-year survival rate of only 6%, pancreatic has been the target for much research on its cause [70]. There are increasing evidence of diet and nutrition playing a key role in development of pancreatic cancer. In this context, dietary intake of folate, present in vegetables and fruits, has generated a lower risk of pancreatic cancer. In contrast, consumption of red meat and saturated fat has been associated with increased risk. Furthermore, a meta-analysis based on 32 studies on pancreatic cancer risk and nutrition was conducted [71]. The outcome was a reduced risk of pancreatic cancer for the category of healthy patterns in comparison to the lowest category. Moreover, a light-moderate drinking pattern demonstrated a lower risk compared to heavy drinking.

In a case-control study nested within the EPIC program, the association of pre-diagnostic plasma levels of carotenoids, vitamin C, retinol (Vitamin A1) and tocopherols (vitamin E) with the risk of pancreatic cancer [72] was examined. Plasma α - and β -carotene, lutein and γ -tocopherol showed heterogeneity between geographical regions. Higher plasma concentrations of β -carotene, zexanthin and α -tocopherol indicated an association with pancreatic cancer risk. The EPIC cohort also conducted a study on the association of a Mediterranean diet and risk of pancreatic cancer [73]. The study included over half a million participants from 10 European countries consisting of a diet without alcohol to discount alcohol-related harmful effects. Overall, the results suggested that there was no association between the Mediterranean diet and risk of pancreatic cancer.

Prevention of Cancer through Diet

Most of the examples presented above relates to therapeutic benefits of dietary interventions. An important aspect is the preventive action which changes in dietary intake can provide. It has been demonstrated that cruciferous vegetables can provide better protection against certain cancers than total vegetable and fruit consumption [74]. In this context, isothiocyanates (ITCs) and selenium possessing anti-oxidant properties have been identified as components generating beneficiary effects. Their actions are based on epigenetic mechanisms including aberrant DNA methylation. Moreover, DNA methylation and histone modification processes have been triggered by bioactive food compounds such as folate, polyphenols, selenium, fatty acids, ITCs and allyl compounds affecting cell proliferation, differentiation and cell death, potentially preventing cancer development [22]. Moreover, high consumption of vegetables from the Brassica family including broccoli has been described to reduce the risk of cancer [75]. The bioactive compounds of broccoli comprise of kaempferol, quercetin, lutein, carotenoids, vitamins and minerals. These compounds can modulate xenobiotic metabolizing enzymes, stress response mechanisms, and protection against genome instability. Additionally, the prevention and progression of cancer may be influenced by the anti-inflammatory, signal transduction and epigenetic mechanisms triggered by broccoli and broccoli extracts. Despite evidence of its chemoprevention of cancer, broccoli consumption has also been described to cause genotoxic activity in animal models [76]. However, these findings have not been confirmed in humans, so the benefits of broccoli consumption in modest quantities seem to outweigh the potential risk of adverse events.

Zinc has been shown to induce cell-mediated immune functions, anti-oxidant and anti-inflammatory activities [77]. As zinc inhibits NF-kappa B, constitutively expressed in cancer cells, zinc supplementation may support chemoprevention by reducing angiogenesis, inducing inflammatory cytokines, and accelerating apoptosis in cancer cells. Additionally, proanthocyanidins can provide chemoprevention through their anti-oxidant, immune- and enzyme-modulating properties [7]. Likewise, the phytoalexin resveratrol has also shown anti-oxidant activity, inhibition of cyclooxygenases, and activation of peroxisome proliferator activated receptor (PPAR) [78]. In a com-

prehensive review, the relationship between apple consumption and human health was described [79]. Consumption of apples and apple juices was associated with reduced risk of cancer and other diseases due to their rich phytochemical profiles. Similarly, the effect of intake of pure apple, cranberry, grape, grapefruit, orange and pomegranate fruit juices has been provocative in relation to cancer prevention, although challenges and unanswered questions remain [80].

Nutrition in Cancer Patients

Although quite a few studies have focused on cancer prevention and evaluation of cancer risk related to dietary intake, attention has also been paid to the nutrition of cancer patients [81]. The risks of under-nutrition and starvation of cancer patients have been recognized in four areas of nutritional interventions including perioperative nutrition in patients subjected to surgery, permissive nutrition in patients receiving chemo- and radiotherapy, home parenteral nutrition and supplemental nutrition in weight-losing patients. Another study indicated that cancer patients showing low concentrations of n-3 fatty acids due to suboptimal intake and metabolic disturbances could achieve improved cancer therapy efficacy and reduced toxicity by dietary n-3 fatty acid supplementation [82].

Low-risk prostate cancer patients not subjected to surgery, radiation or hormonal treatment were placed on a Mediterranean-style diet and change in lifestyle for evaluation of gene expression profiles after 3 months [83]. The study showed up-regulation of 48 genes and down-regulation of 453 genes, comprising of genes related to protein metabolism, intracellular protein traffic and phosphorylation, essential for carcinogenesis. Furthermore, significant improvements in treatment of obesity, blood pressure and lipid profiles were observed. The two year follow-up Prostate Cancer Lifestyle Trial in early-stage prostate cancer patients, which had been subjected to dietary modifications and lifestyle changes, revealed a potential avoidance or delay of conventional treatment for two years [84]. In another study on prostate cancer patients, the potentially chemopreventive effect of green tea consumption was compared to black tea and water intake [85]. Prostate tumor markers for cancer development and progression for proliferation (Ki67), apoptosis (Bcl-2, Bax, Tunel), inflammation (NFκB) and oxidation (8-hydroxydeoxy-guanosine (8OHdG)) were monitored as primary endpoints. Urinary oxidation, tea polyphenol uptake in prostate tissue, and prostate serum antigen (PSA) comprised the secondary endpoints. No significant difference in markers of proliferation, apoptosis and oxidation was seen in prostate tissue after consumption of green tea, black tea or water. Tea polyphenols were detected in prostate tissue from 32 of 34 patients after green tea consumption, but not black tea or water. The anti-oxidant effect was only seen after green tea intake. Similarly, a small but statistically significant decrease in PSA levels was detected after green tea consumption.

The issue of adequate nutrition as part of good quality of life was addressed in children with cancer [88]. To avoid malnutrition, close interaction between pediatric oncologists and nutrition specialists is essential. Another problem occurring in cancer patients relates to zinc deficiency, which may lead to oxidative stress and chronic inflammation [77]. For instance, zinc deficiency was detected in 65% of head and neck cancer patients, which also was a good indicator of tumor burden and stage of disease.

Personalized Medicine

Genomics research has clearly confirmed the differences in therapeutic responses seen from one individual to another. Nutritional intake has also provided different responses in cancer treatment due to genetic and epigenetic mechanisms. In this context, severe symptoms which prevented chemo- and radiotherapy of a breast cancer patient could be linked to nutritional deficiencies based on special testing for metabolic, gastrointestinal and immunologic functions [87]. Nutritional interventions resolved the debilitating symptoms and allowed the patient to be subjected to the necessary chemo- and radiotherapy treatment. Furthermore, nutrigenomics has allowed tailoring of food according to individual genotypes [88]. In this context, the importance of synergistic administration of nutraceuticals has become clear through the action of phytonutrients in prostate cancer prevention and treatment. Similarly, for treatment of *Helicobacter pylori*-related gastric cancer, nutrigenomics approaches have identified those individuals responding to Korean red ginseng treatment [89]. As accumulated nutrigenomics information is collected, it will be possible to better understand the effect of diet on health and disease, which will allow to increase the nutritional quality of individual foods and to provide advice on personalized diets [90].

Another example relates to accurate prediction of the risk of developing severe gastrointestinal toxicity in cancer patients [91]. Recently, increasing focus has been dedicated to the gut microbiome and its impact on treatment-induced gastrointestinal toxicity and tailored treatment regimens based on personalized risk assessment. Moreover, the potential of probiotic bacteria related to the interaction between dietary intake and the immune system has been given more attention with the advances in understanding the effects by the gut microbiota [92]. Beneficial applications of probiotics and advances in development of novel probiotic-based treatment and personalized diets might be of great significance in future cancer prevention and therapy. Protein calorie malnutrition causes weight loss in cancer patients characterized by the cancer anorexia-cachexia syndrome (CACS), which results in loss of muscle with or without loss of fat mass [93]. Therefore, cachexia presents nutritional challenges to prevent severe morbidity and mortality and has triggered the application of personalized medicine to withstand the toxic effects in cancer therapy.

Related to gene-diet interactions, the dietary nutrient intake of participants in the Personalized Medicine Research Project (PMRP) was evaluated in relation to smoking status and the apolipoprotein E4-a (APOE4-a) genetic marker [94]. The study showed that food energy, total fat, cholesterol, protein and alcohol intake decreased with age in both females and males. The macronutrient intake was higher in female smokers, whereas the male nonsmokers had higher intake. Nonsmokers of both genders used more dietary supplements. A possible correlation between the use of supplements and the APOE4 gene was suggested. The dietary data from the PMRP will benefit studies on gene-environment interactions related to disease development. Although genetic determinants aid in personal genotyping and can support the development of personalized diets, a number of other factors such as life style, age, prior nutritional and physiological variables and the composition of the gut microflora provide substantial contributions [95].

Finally, the importance of the influence of dietary phytochemicals on epigenetic mechanisms in relation to personalized diets should not be overlooked. Dietary phytochemicals have been demonstrated to modulate DNA methylation, histone modifications and non-coding miRNA expression [96]. In this context, phytochemicals participate in DNA damage repair by enhancing histone acetylation, aid in restraining cell death and in alteration of DNA methylation. As epigenetic aberration contribute to cancer development and epigenetic biomarkers reveal individualized traits, personalized nutrition will contribute to the prevention of various types of cancer.

Conclusions

In summary, various studies have confirmed the association between dietary intake and risk of cancer development. Generally, dietary intake of fruits and vegetables has presented a reduced cancer risk. A closer characterization has suggested that for example folate, flavonoids, isoflavones, proanthocyanidins and catechins have provided favorable effects. Moreover, consumption of fish, vitamins (prominently present in fruits and vegetables) and coffee has lowered the cancer risk. In contrast, diets rich in red meat have demonstrated an increase in cancer risk. However, some of the findings are contradictory and additional large population studies are needed. Dietary interventions have provided both prophylactic and therapeutic effects against various cancers. The mechanisms of action vary from one bioactive compound to another. For instance, PUFAs affects carcinogenesis by suppression of arachidonic acid-derived eicosanoid biosynthesis, influences transcription factor activity, gene expression and signal transduction, alters estrogen metabolism, increases or decreases production of free radicals and reactive oxygen species and involves insulin sensitivity and membrane fluidity [97]. Moreover, the action of extracts of *C. setidens* and *A. scaber* occurs through down-regulation of MAPK pathways and up-regulation of anti-oxidant genes associated with cancer development. Additionally, the importance of taking into account special nutritional requirements for cancer patients has been addressed. Recent progress in omics research including genomics, proteomics, metabolomics, and nutrigenomics has opened up possibilities for the design of personalized diets, which will have substantial impact on both prevention of cancer and individual treatment of cancer patients. Finally, the significant influence of nutrition on epigenetic mechanisms and its effect on cancer prevention and therapy cannot be neglected [98]. An interesting aspect is also how the many plant species and extracts commonly used for hundreds of years in traditional medicine seem to find a new niche in modern Western medicine and drug development. Thorough and genuine evaluation of these compounds in well planned and executed clinical trials will further provide evidence of the importance of nutritional interventions in cancer therapy.

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