

Cancer and Diet

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Abstract: Intervention in food intake has been demonstrated to play an enormous role in both prevention and treatment of disease. Numerous studies indicate a clear link between cancer and diet. The substantial development of sequencing technologies has resulted in access to enormous amounts of genomics information, which resulted in the establishment of nutrigenomics as an emerging approach to link genomics research to studies on nutrition. Increased understanding has demonstrated how nutrition can influence human health both at genetic and epigenetic levels. Dramatic dietary modifications have proven essential in reducing risk and even prevention of cancer. Moreover, intense revision of diet in cancer patients has revealed significant changes in gene expression and also has provided therapeutic efficacy even after short-term application. Obviously, a multitude of diets have been evaluated, but probably the common factor for achieving both prophylactic and therapeutic responses is to consume predominantly diets rich in fruits, vegetables, fish and fibers and reduced quantities of especially red meat. Despite encouraging findings on how dietary modifications can prevent disease and restore health, there are a number of factors which complicate the outcome. There are variations in response to dietary changes depending on age and gender. Furthermore, ethnic, social and geographic circumstances play an important role.

Keywords: Nutrigenomics, epigenetics, DNA methylation, microRNA, dietary modifications, lifestyle changes, personalized nutrition, disease prevention, therapeutic nutrition.

INTRODUCTION

Cancer is one of the most devastating and wide-spread diseases today. The development of cancer is a multi-step process involving genetic or epigenetic changes often occurring over a longer period of time [1]. Moreover, cancer occurs in more or less all organs and tissues and is characterized by extensive heterogeneity both concerning the type and aggressiveness of the disease. Although some substantial progress in some areas has been made, there are still huge unmet needs in treatment methods and the efficacy of currently available drugs. The pharmaceutical industry has struggled with the ever increasing costs in drug development and unfortunately novel drugs have not seldom demonstrated only marginal improvement in efficacy often at the cost of quality of life of the patients. For these reasons, new approaches are focusing on disease prevention instead of only treating the symptoms. Recently, much attention has been paid to prevention of the disease in parallel to continuous drug discovery.

Interestingly, food intake has been shown to have a substantial influence on disease development and not the least cancer. More than thirty years ago it was suggested that diet accounted for about a third of the risk of developing cancer in the US [2]. Later, The World Cancer Research Fund and American Institute of Cancer Research Report concluded after reviewing

thousands of publications that diet provides a significant contribution to cancer globally [3]. Another study suggests that most likely over two-thirds of cancer-related deaths could be prevented by nutritional intervention and lifestyle changes [4]. There are numerous investigations into both preventive and therapeutic influence of nutrition and its relationship to cancer. Recent major development in genomics and other omics research has provided valuable insight into understanding the interaction between nutrition and cancer. Especially the incredible improvement in sequencing technologies has enabled access to massive amounts of data and has also led to the birth of nutrigenomics, the science investigating the effects of nutrition and bioactive food compounds on gene expression [5]. This approach has allowed the investigation of the effect on nutrition on individuals with specific genetic features. Moreover, it has provided the basis for nutritional intervention in prevention and treatment of disease and the inauguration of personalized nutrition. However, differences in types of cancer, the level of aggressiveness, and their occurrence at different stages of life have seriously complicated the understanding of the effect of nutrition on cancer prevention and treatment. Other individual variations such as the amounts of food consumed, digestion, metabolism and other factors like geographical, ethnic and sociological diversity has hampered the identification of which food components are most important for human health [6, 7]. In this review, the effect of nutrition on genetics and epigenetics is discussed. Furthermore, examples of preventive and

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therapeutic influence by nutritional intervention for different cancer indications are described.

GENETICS AND EPIGENETICS

The most common genetic variations affecting gene expression are point mutations often related to single nucleotide polymorphisms (SNPs) [8]. Additionally, deletions [9], insertions [10], and copy number variations [11] generate genetic heterogeneity. Also transposons can behave as mutagens because of causing disruption or misplacement of functional genes [12]. Epigenetics counts for mechanisms outside the scope of conventional genetics [1]. Epigenetic modifications do not take place in the primary DNA sequence, and are therefore potentially reversible, which makes them attractive targets for therapy. The most common modifications comprise DNA methylations [13], histone modifications [1] and RNA interference [14]. DNA methylations have been linked to reduction or cessation of mRNA transcription, but can also generate up-regulation. In this context, hypermethylation in promoter regions can inactivate tumor suppressor genes such as HIC1, INK4b and TIMP3 [15]. Histones, particularly histones H3 and H4 are modified by acetylation, methylation, ubiquitination and phosphorylation [16], which can lead to transcription activation or repression [17]. In the context of RNA interference, the 21-23 nucleotide long single-stranded microRNAs interfere with mRNA [18] resulting in down-regulation of gene expression [19]. A number of miRNAs have been associated with cancer [18, 20].

Due to epigenetic reversible deregulation in early carcinogenesis, bioactive food compounds such as folate, polyphenols, selenium, and retinoids can influence DNA methylation and histone modification processes and thereby provide cancer prevention [21]. Moreover, epigenetic alterations contributing to aberrant miRNA expression and enhanced cancer risk might be reversed by nutritional modifications [22].

DIET AND CANCER

There are numerous examples of indications that nutrition has a strong influence on cancer both in preventive and therapeutic aspects. However, genetic, ethnic, sociological and geographical variations in the target population, difficulties in monitoring dietary changes, and interpretation of beneficiary effects have made it difficult to evaluate the true value of the link between diet and cancer. Despite this confusion a number of meta-analysis have been conducted and additional verified examples do exist to strongly support

the beneficiary effects of nutritional interventions for prevention and treatment of various cancers. Several examples are given for different cancer indications below and are also summarized in Table 1.

Breast Cancer

Because the results from several studies on the reduced risk of fiber intake for breast cancer have been inconclusive a meta-analysis of prospective cohort studies was carried out [23]. Ten studies were included in the meta-analysis including 712,195 participants. There was no significant difference in geographical regions, length of follow-up, or menopausal status of the individuals for the association between dietary fiber intake and risk of breast cancer. In conclusion, a significant inverse dose-response association between dietary fiber intake and breast cancer risk was obtained. Another meta-analysis study investigated the risk of breast cancer and dairy consumption [24]. The prospective cohort studies included more than one million participants. The conclusion was that increased consumption of total dairy food, excluding milk, may be associated with a reduced risk of breast cancer. Likewise, inconsistency has hampered studies on soy consumption and risk of breast cancer. A meta-analysis of 4 studies on breast cancer recurrence and 14 studies on breast cancer incidence was conducted [25]. The outcome suggested that soy isoflavone intake is associated with a significantly reduced risk of breast cancer incidence in Asian populations. However, it was not the case in Western populations. In another study the association of olive oil intake and risk of breast cancer in post-menopausal women was investigated [26]. The analysis of 62,284 women in the Mediterranean showed no association between olive oil consumption and the risk of estrogen or progesterone receptor-positive tumors. Promising results have been obtained to lower the risk of breast and ovarian cancer among BRCA1 carriers by optimizing the selenium concentration in the diet [27]. Novel studies will be conducted on 1500 BRCA1 carriers for a three year follow-up study.

Prostate Cancer

In exploration of previously described anti-cancer properties of green tea extracts, severe combined immunodeficiency (SCID) mice with human LAPC4 prostate tumors were administered brewed tea instead of drinking water [28]. The SCID mice showed a significant decrease in tumor volume and tumor size correlated with green tea polyphenol contents in tumor tissue. The mechanism of green tea polyphenol is

Table 1: Cancers Affected by Nutrition

Cancer Type	Nutrition / Source	Effect	Ref
Breast	Dietary fiber	Meta-analysis on reduced cancer risk	[23]
	Dairy products (not milk)	Meta-analysis on reduced cancer risk	[24]
	Soy isoflavones	Reduced cancer risk in Asian women	[25]
	Olive oil	No association with olive oil and cancer risk	[26]
	n3 fatty acids	Benefits in breast cancer patients	[51]
Colon	Vegetables, fruits	Reduced risk of cancer	[38]
	Myrosinase hydrolysate, broccoli	Reduced risk of colon cancer	[43]
Esophageal	Vegetables, fruits	Decreased risk of esophageal carcinoma	[36]
	Vegetables, fruits	Prevention against cancer	[39]
Gastric	Vegetables, fruits	Prevention against cancer	[39]
Head & neck	Zinc	Beneficial effects on cancer	[45]
Prostate	Polyphenols, green tea	Inhibition of tumor xenograft growth in mice	[27]
	Polyphenols, Nigerian foodstuffs	Chemoprevention of prostate cancer	[28]
	Sulforaphane, tea polyphenols	Prevention of prostate cancer	[31]
	Curcumin, allyl sulfur	Prevention of prostate cancer	[31]
Skin	Folate	Protection of sun-exposed skin from cancer	[32]
	Epicatechins, green tea	Chemoprevention of carcinogenesis	[34]
	Proanthocyanid, grape seeds	Chemoprevention of carcinogenesis	[34]
	Vitamin D	Reduction in mortality	[33]

believed to act through inhibition of oxidative stress and angiogenesis. In another study, the effect of Nigerian foodstuffs on prevention of prostate cancer was investigated [29]. Nigerian food includes *Dacryodes edulis*, *Moringa oleifera* and *Syzygium aromaticum* containing polyphenols like ellagic acid, gallate, methylgallate, kaempferol and quercetin. Moreover, the diet comprises soy beans (isoflavones), chili pepper (capsaicin), and green tea (epicatechin). Taking advantage of these beneficiary compounds can therefore potentially provide prevention and reduction of the high incidence of prostate cancer in Nigeria and other African countries.

In another study, low-risk prostate cancer patients, who had not been subjected to surgery, radiation or hormonal treatment, received a modified diet and they were subjected to change in lifestyle [30]. The outcome was a significant improvement in treatment of obesity, blood pressure and lipid profile. Gene expression profiles were monitored from RNA samples before and three months after the intervention. Forty-eight genes were up-regulated and 453 were down-regulated. Change in gene expression was observed in protein metabolism, intracellular protein traffic and phosphorylation. Moreover, results from a two year

follow-up study in early-stage prostate cancer patients undergoing lifestyle and dietary changes (Prostate Cancer Lifestyle Trial) [31] showed a potential avoidance or delay of conventional treatment for two years. Furthermore, epigenetic alterations including DNA methylation, histone modifications and interfering miRNAs are responsible for dysregulation of gene expression and therefore important factors for the development of cancer [32]. Specific nutrients and food components such as folate, vitamin B12, selenium, zinc as well as phytochemicals (sulforaphane, tea polyphenols, curcumin, and allyl sulfur compounds) present agents involved in epigenetic modifications and might be targets for chemoprevention for prostate cancer.

Skin Cancer

As increased exposure to UV light has resulted in an enhanced frequency of skin cancer, means of preventive measures have been investigated. It has been demonstrated that both vitamin D and folate play an important role in skin pigmentation balance. Due to its involvement in DNA repair, folate has been proposed as a factor involved in cancer prevention and recent studies have indicated a critical role in the protection of sun exposed skin [33]. In another study,

the reduction in mortality rates of cardiovascular disease and cancer were estimated after doubling vitamin D levels [34]. The results showed that increase in 25(OH) D levels was the most cost-effective way to reduce global mortality.

Bioactive dietary components such as epicatechins from green tea and proanthocyanidins from grape seeds have been evaluated in animal models in chemoprevention of UV-induced skin cancer [35]. Their mechanism seems to be epigenetic by blocking UV-induced DNA hypermethylation and histone modifications generally required for the silencing of Cip1/p21 and p16 INK4a tumor suppressor genes.

Stomach Cancers

Diet rich in vegetables and fruits has been evaluated on the risk of gastric and esophageal cancer [36]. In this study a statistically significant inverse association with the risk of esophageal squamous cell carcinoma was observed, which was independent of consumed quantity and variety of vegetables and fruits. Moreover, it has been revealed that tea and particularly green tea with high concentrations of anti-oxidants can contribute to the prevention of different cancers such as stomach esophageal, ovarian and colon cancers [37]. In a case-control study in Western Australia, the consumption of fruits and vegetables in relation to the risk of colon and rectal cancers was evaluated [38]. The results suggested that the risk of proximal colon cancer and rectal cancer was not associated with the intake of total vegetable and fruit. In this context, Brassica vegetable intake was inversely related with proximal colon cancer. Similarly, distal colon cancer risk was significantly lower after consumption of dark yellow vegetables and apples.

In another study, the association of vegetable and fruit intake and the risk of esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), gastric cardia adenocarcinoma (GCA), and gastric noncardia adenocarcinoma (GNCA) was investigated [39]. The Dutch cohort study initiated in 1986 was followed up after 16 years. A significant inverse association between raw vegetable consumption and EAC risk was observed. A similar association was obtained between Brassica vegetables and GCA risk. Moreover, citrus fruit intake was inversely associated with EAC and GCA risks. Interestingly, especially smokers demonstrated an inverse correlation between vegetable and fruit intake and ESCC and EAC risks.

PREVENTION OF CANCER THROUGH DIET

Although examples have been given above for therapeutic benefits of dietary intervention additional examples and also their preventive action are described in this section. In this context, epidemiological studies have indicated that cruciferous vegetables can provide more efficient protection against certain cancers than total fruit and vegetable consumption [40]. Isothiocyanates (ITC) and selenium have been identified as components providing beneficiary effects, particularly related to their anti-oxidant properties. It has been demonstrated that ITC and selenium influence epigenetic mechanisms through their effect in aberrant DNA methylation and thereby modulation of gene-specific and global methylation patterns. Another study, indicated that bioactive food compounds such as folate, polyphenols, selenium, retinoids, fatty acids, ITCs and allyl compounds affect gene expression through DNA methylation and histone modification processes [21]. As the target genes are involved in cell proliferation, differentiation and cell death they potentially provide an important impact on cancer prevention. Likewise, it has been shown that micronutrients such as folate, vitamin B12, selenium and zinc affect epigenetic events such as DNA methylation, histone modification and miRNA expression [41]. Moreover, phytochemicals such as sulforaphane, tea polyphenols, curcumin and allyl sulfur compounds affect epigenetic dysregulation, which alters gene expression and presents significant influence on prostate cancer progression.

Furthermore, high intake of vegetables belonging to the Brassica family such as broccoli has been suggested to reduce the risk of cancer [42]. Glucosinolates, plant pigments such as kaempferol, quercetin, lutein and carotenoids as well as various vitamins and minerals are bioactive chemicals present in broccoli, which may act through the modulation of xenobiotic metabolizing enzymes, NF-E2p45-related factor-2 (Nrf2)-mediated stress response mechanisms, and protection against genomic stability. Moreover, broccoli and broccoli extracts might influence the progression of cancer through anti-inflammatory effects, impact on signal transduction, epigenetic modulations and influence on the microflora in the colon. In another study, liquid chromatography-electrospray ionization (LC-ESI) was applied to identify aqueous extracts of *Brassica oleraceae L. Var. italia* [43]. Crude extracts of broccoli florets showed strong inhibition of human colon cancer cell lines. Furthermore, myrosinase hydrolysate demonstrated 95% lethality in the same colon cancer cell lines.

Although evidence of chemopreventive effects of consumption of broccoli has been described, recent *in vitro* animal studies indicate that broccoli and glucosinolate-derived degradation products potentially show genotoxic activities [44]. However, the relevance of these findings has not been confirmed in humans. For the time being, it seems that the benefits of consumption of modest quantities of broccoli outweigh the potential risk.

Zinc deficiency has previously been associated with growth retardation and cognitive impairment, but more recently zinc has been shown to improve cell-mediated immune functions and can also act as an anti-oxidant and anti-inflammatory agent [45]. Zinc has been demonstrated to inhibit NF-kappa B, which is constitutively activated in many cancer cells. Therefore, zinc supplementation can decrease angiogenesis and induction of inflammatory cytokines and simultaneously accelerate apoptosis in cancer cells and thereby provide an approach for cancer chemoprevention. Furthermore, proanthocyanidins which are abundant in plants have demonstrated positive cardiovascular activities and have more recently been associated with cancer chemoprevention [46]. Proanthocyanidines are postulated to act through their anti-oxidant, immune- and enzyme modulating properties and could be supplied as safe dietary compounds. Another compound, resveratrol has been identified as a phytoalexin, which functions as an anti-oxidant, cyclooxygenase inhibitor, and peroxisome proliferator-activated receptor [47]. As resveratrol is a component of grapes appropriate long-term drinking of red wine has been associated with a reduced risk for cardiovascular disease and cancer. Moreover, meta-analysis has suggested a positive association between flavonoid consumption and cancer prevention as they affect anti-oxidation, anti-inflammation and effects on NK cells [48]. In relation to cancer treatment flavonoids present pro-oxidant capacity and particularly methoxylated flavonoids possess favorable pharmacokinetic properties. Interestingly, a recent comprehensive review studied the relationship between consumption of apples and apple components and human health [49]. Intake of apples, apple juices and their rich phytochemical profile has been associated with reduced risk of cancer, cardiovascular disease, asthma and Alzheimer's disease through various mechanisms including anti-oxidant, anti-proliferative and cell signaling effects.

NUTRITION IN CANCER PATIENTS

Not only the general population, but also cancer patients can significantly profit from modifications in

dietary intake. For example, attention has been paid to the risks of starvation and under-nutrition in cancer patients [50]. In this context, four areas of nutrition intervention have been recognized including perioperative nutrition in patients subjected to surgery, permissive nutrition in patients receiving chemotherapy and radiation therapy, home parenteral nutrition and supplemental nutrition in weight-losing patients. Moreover, cancer patients often show low concentrations of n-3 fatty acids because of suboptimal intake and metabolic disturbances and n-3 supplementation has demonstrated improved efficacy and reduced toxicity of cancer chemotherapy [51]. This suggests that fish oil can provide broad therapeutic potential in cancer patients.

Although several clinical trials have indicated the importance of adequate nutrition to treatment response and quality of life in cancer patients, less attention has been paid to pediatric oncology [52]. It is therefore very important to prevent malnutrition in children with cancer. Close interaction is therefore needed between pediatric oncologists and nutrition specialists to address current shortcomings in childhood cancer. Moreover, oxidative stress and chronic inflammation due to zinc deficiency have been suggested to be associated with many cancers. For instance, 65% of head and neck cancer patients showed zinc deficiency based on cellular zinc measurements [45]. The zinc status was a good indicator of tumor burden and stage of disease. There was also a correlation with the number of hospital admissions and incidences of infections.

More as a curiosity, the impact of the adaptation of ice cream as a nutritional supplement in cancer patients on quality of life was investigated [53]. Ice cream was adapted as a nutrition supplement in cancer patients with malnutrition disorders. The outcome was a significant reduction in anxiety and depression compared to the control group and therefore covered in part the social aspect of food and improved quality of life in malnourished cancer patients.

PERSONALIZED NUTRITION

Data derived from genomics research has clearly indicated the importance of personal differences to obtain improved efficacy in disease treatment. Likewise, individual genetic and epigenetic differences have been shown to provide the basis for variations in the effect of nutrition in cancer patients. A case-report on a breast cancer patient demonstrated how the severe symptoms did not fit any clear disease pattern

and prevented chemotherapy and radiation treatment [54]. Important nutritional deficiencies were discovered through specialized testing for metabolic, gastrointestinal and immunologic functions. This allowed nutritional intervention, which resolved the debilitating symptoms of the patient and allowed her to be subjected to the necessary chemotherapy and radiation.

In the context of nutrigenomics, tailoring of food according to individual genotype has become a reality [55]. For instance, the mechanisms of action of phytonutrients and potential effects on prostate cancer have revealed the importance of synergistic administration of nutraceuticals. Similarly, efforts were made to discover *Helicobacter pylori*-related disease biomarkers, which could be applied for diagnostic, predictive and therapeutic purposes [56]. In this context, a nutrigenomics approach allowed confirmation of the efficacy of Korean red ginseng prevention of *H. pylori*-associated gastric cancer.

Accumulated nutrigenomics information can provide a better understanding of the effect of diet on health and has resulted in steps of increase in nutritional quality of individual foods and provision of personalized diet advisory [57]. Although some genetic determinants will aid in personal genotyping it will not be the solution to personalizing diet and health. Instead a number of other factors such as the stage of life, lifestyle, prior nutritional and physiological variables and even the composition of the gut microflora provide significant influence [58]. Therefore, such technologies as imaging, proteomics and metabolomics will provide tools for better understanding and assessment of nutritional phenotypes of individuals.

CONCLUSIONS AND FUTURE PROSPECTS

There are numerous examples of how dietary intake can promote health on both a preventive as well as therapeutic level. Radical change in diet has resulted in dramatic changes in gene expression in prostate cancer patients [30] revealing that many of those genes involved in cancer development were down-regulated. The importance of nutrigenomics as a multi-task approach involving genomics, proteomics, metabolomics, et cetera has further provided novel possibilities to address the effect of nutrition on human health. However, the vast amount of accumulated nutrigenomics data should not overshadow the needs to take into account other important factors such as lifestyle, social, geographical and economic factors affecting diet and health.

In summary, it would obviously be of great importance if some general recommendations could be established in the form of dietary counselling for cancer patients. However, due to the individual differences and variability in the types and stages of cancer, it is most likely an impossible task. Despite that as described above, several examples of diets based on high content of vegetables and fruits (Mediterranean, Ornish diet, ect.) have proven successful in providing benefits for health and quality of life.

It is appropriate to end this review on a high note. As explained above, dietary modifications can have profound effects on health by reducing the risk of disease and even reversing existing maladies. As a recent study indicated, red meat consumption is clearly associated with increased risk in cardiovascular and cancer mortality [59]. Moreover, as the global livestock sector consumes more than 40% of world grain and generates more greenhouse emission than transportation, a dietary change is also beneficial for our planet [60].

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