Nutrition and Disease

Nutrition and Disease:

Prevention and Therapy

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CHAPTER 1

INTRODUCTION

Nutrition has always played an important role in the lives of humans and domestic animals. In combination with shelter against weather and predatory dangers, it has been the cornerstone to guaranteeing survival and continuation of life in general. The nature and type of nutrition in relation to health had already received attention in the nineteenth century with the saying that "you are what you eat" [1, 2]. More recently, active research on nutrition and diet has further strengthened the association between food intake and health. Nutrition can therefore reduce the risk of, or even prevent disease as well as act as therapeutics [3]. A quick search in PubMed with the terms "nutrition" and "disease" generated 424,781 hits (accessed on December 15, 2019)! The risk of disease has been demonstrated to be significantly reduced after changes in nutritional habits and introduction of lifestyle modifications. Likewise, patients with an existing disease have experienced significant improvement by switching to a modified diet. In another approach, traditional medicines based on plants and plant components have for centuries provided treatment for a large variety of indications all over the world [4]. Unfortunately, the outcome has often relied on anecdotes and word of mouth and has rarely been subjected to serious scientific evaluation. However, during the last decade a shift toward science-based validation of traditional medicines in randomized controlled clinical trials has taken place. Very recently, major developments in bioinformatics, genomics and proteomics research have generated new insights into the relationship between nutrition and disease not least through the introduction of nutrigenomics, the field studying the interaction of nutrition and gene expression [5]. During the past five to ten years, the effect of nutrition on epigenetic mechanisms and their association with risk of disease development and prevention has been widely confirmed. Interestingly, the impact of nutrition on drug development has proved to be significant, especially in times when personalized medicine has become a reality. However, most importantly, the determination of the association between nutrition and disease is highly complicated for the following reasons. Dietary intake is often based on questionnaires and is certainly difficult to control. Unless the study is conducted on hospitalized patients it

will be almost impossible to verify the actual food intake. However, recent web-based instrumentation and photographical documentation of dietary intake have improved the monitoring. Moreover, when studying the effect of a specific nutritional component it is difficult to evaluate the input from other dietary factors and their potential interaction. Additionally, there are many controversial findings of positive or negative effects of specific dietary components, which need to be further addressed through thorough and sound scientific analyses. Finally, social and ethnic factors play a significant role that should not be neglected.

Scope of the Book

This book describes the relationship between nutrition and disease from various aspects. The aim is to give an overview of the complicated interaction between dietary intake and prevention, development, and treatment of disease. Examples are presented for the major disease indications such as cancer, neurological disorders, and metabolic, cardiovascular, and infectious diseases. Moreover, recent scientific discoveries of the fascinating association of nutrition with genetic and epigenetic mechanisms, and the link to disease will be discussed.

Although a deep understanding of molecular biology and genetics is required to fully appreciate the detailed information in the book, the goal is to also target a wider audience with a general interest in nutritional input and scientific issues. For this reason, at the end of each chapter a paragraph is dedicated to “the layman’s view” supported by some illustrations.

Summary

In conclusion, the substantial influence of nutrition on human health has been further confirmed by both epidemic and molecular findings. The association of nutrition with the risk of cancer, neurological disorders, metabolic, cardiovascular, infectious, and other diseases has been scientifically evaluated. Moreover, the effect of dietary intake and lifestyle changes can present a significant impact on human health, and therapeutic efficacy in patients with various diseases. Recent epigenetics research has demonstrated a strong link between nutrition and modified epigenetic functions, with a substantial impact on human disease. The reversible nature of epigenetic modifications has also attracted drug development efforts based on epigenetics. Additionally, plant-based and natural products have

received increased attention not only where applied in traditional medicines, but also as part of modern science-based development.

Layman's View

In summary, nutrition plays an important part in relation to disease risk (Fig. 1.1). Dietary intake has demonstrated a strong influence on prevention and treatment of various diseases. For centuries, traditional herbal medicines have been applied for many different ailments. Although treatment efficacy has been claimed, until recently it has not been supported by scientific data. However, increased interest in plant-based drugs including clinical evaluations has provided more credibility to the field recently. At the same time, progress in genomics and nutrigenomics research has generated insight into how nutrition can affect human health on the gene level, either directly by the introduction of changes in the primary DNA sequence or reversibly through epigenetic modifications.

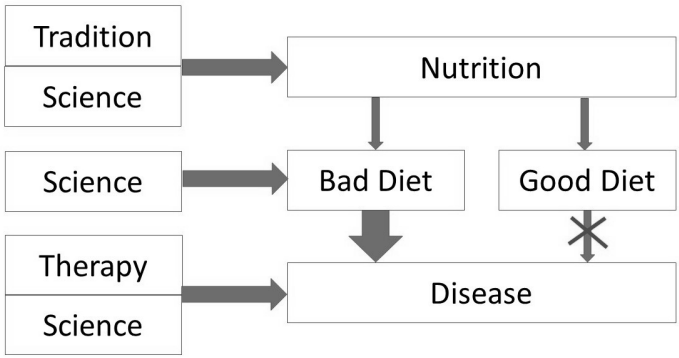

Fig. 1.1. Illustration of the interaction of nutrition and disease influenced by science and tradition.

References

1. Brillat-Savarin, A. In *Physiologie du Gout, ou Meditations de Gastronomie Transcendante* **1826**.
2. Feuerbach, LA. *Concerning Spiritualism and Materialism* **1864**.
3. Lundstrom K. Past, Present and Future of Nutrigenomics in Drug Development. *Curr Drug Discov Technol.* **2013**, *10*, 35-46.

4. Jiao, Y, Wickett, NJ, Ayyampalayam, S, et al. Ancestral polyploidy in seed plants and angiosperms. *Nature* **2011**, *473*, 97-100.
5. Lundstrom, K. Epigenetics, Nutrition, Disease and Drug Development. *Curr Drug Discov Technol.* **2019**, *16*, 386-391.

CHAPTER 2

NUTRITION AND DISEASE

Abstract

The influence of nutrition on health from both preventive and therapeutic aspects has been documented by epidemiological data and meta-analyses. However, the importance of ethnic and social factors related to dietary habits should not be underestimated. In any case, there are various studies indicating that nutrition plays an important role in disease risk for numerous indications in the fields of cancer, metabolic, cardiovascular, infectious diseases, and neurological disorders. This chapter provides an insight into epidemiological studies and gives examples of how nutrition can have a positive effect on reducing the risk of disease development, and how change in dietary intake can be of therapeutic value.

2.1. Influence of Nutrition on Health

There are clear indications that there is a strong link between dietary intake and health [1]. In numerous cases, data from epidemiological studies and meta-analysis provide support for this statement. However, defining a specific effect of nutrition is a difficult task as many factors contribute to the development or prevention of disease. Synergistic and inhibitory effects of nutritional components also need to be addressed. Moreover, social aspects and ethnic factors should not be excluded when evaluations of the effect of nutrition are discussed.

2.1.1. Epidemiological Data

The vast amount of data accumulated from epidemiological studies makes it necessary in the context of this chapter to focus on nutritional epidemiology. As a subdiscipline of epidemiology, nutritional epidemiology provides specific information of nutritional science [2]. The field deals with dietary assessment, description of nutritional exposure, and statistical modeling of diet–disease relationships. There is now a trend to replace food

frequency questionnaires with short-term quantitative instruments for dietary assessments with the aim to prevent potential gross measurement errors. Moreover, web-based instruments for self-administration have been introduced in place of costly interviews. Attention has also been paid to improved documentation of dietary intake by photography. Furthermore, standardization of food coding aims at improving study comparability. In the context of bioactive substances, novel high-throughput mass spectrometry has been applied for measurements in body fluids. Much attention has also been paid to statistical modeling of dietary data, which has allowed conversion of quantitative short-term measurements into habitual individual intake. Additionally, substitution modeling should be preferred in place of simple adding modeling.

One aspect of nutritional epidemiology relates to missing values and outlier data [3]. Difficulties in collecting data in dietary surveys due to the lack of data on food consumption, poor food description, and inadequate data processing have resulted in missing data and misinterpretation of the results. In this context, software development and statistical analysis methods can provide support for dealing with missing values to execute deletion methods, simple imputation, and multiple imputation. Another approach to optimize nutritional epidemiological studies involves elements of design, interpretation, and communication of nutritional surveys to enhance and encourage the production of reliable and objective evidence [4]. Therefore, developing guidelines and policies with better transparency of research, raw data, and data analysis will facilitate epidemiological studies.

An interesting aspect of nutritional epidemiology relates to microsimulation studies on how to possibly improve health by supporting food purchases [5]. Application of the CVD-PREDICT microsimulation model to the Supplemental Nutrition Assistance Program (SNAP) between 2009 and 2014 subjected to meta-analysis on food pricing and diet–disease effects, has revealed impacts on dietary policy interventions. These comprise a 30% incentive for fruits and vegetables, a combination of fruit and vegetable incentives and restriction of sugar-sweetened beverages, and a broader incentive/disincentive program for multiple foods including nuts, whole grain, fish, and plant-based oils (incentives) and junk food and processed meat (disincentives). The simulation suggested that among 14.5 million adults subjected to fruit and vegetable incentives over five years, 38,782 cardiovascular disease events were prevented and 18,928 quality-adjusted life years were gained. Moreover, $1.21 billion was saved in healthcare costs. Additional restrictions of sugar-sweetened beverages increased the prevention of cardiovascular disease events to 93,933, leading to the gain of

45,864 quality-adjusted life years, and a saving of $4.33 billion. Lifetime simulation suggested that more than 300,000 cardiovascular events can be prevented, almost 650,000 quality-adjusted life years gained, and $6.77 billion saved in healthcare costs. In summary, healthier eating as modeled by SNAP could provide substantial health benefits and significant savings in healthcare costs.

Concerning future aspects of epidemiology, a glance at five high-impact epidemiological journals indicated that the main topics addressed infectious disease and cardiovascular disease epidemiology in publications between 1974 and 2013 [6]. Cancer epidemiology was a favorite topic during 1974–2001, but its popularity decreased thereafter. However, recent claims that nutrition epidemiology of cancer is dead have been challenged by studies particularly indicating the association between plant foods and reduced cancer risk as described in more detail below (see 2.2.1. Nutrition and Cancer) [7]. Nutritional epidemiology gained importance from 1974 to 2014. Analysis of the contents of six high-impact general medicine journals showed similar results to those of epidemiological journals.

2.1.2. Social Aspects of Nutrition

It is extremely important not to underestimate the social aspects of nutrition, and nutritional behavior should be investigated from the sociocultural point of view [8]. Due to the social nature of man, deep-rooted habits have developed within different cultures, resulting in wide variation in different societies. The sociocultural factors include food production, processing, and cooking, but also social behavior related to food consumption [9–13]. Despite the strong global effect of Western industrial civilization, local sociocultural aspects still play an important role in dietary habits in different cultures. In this context, the influence of group size and gender composition was studied in lunch and dinner settings for 469 individuals in three large university cafeterias [9]. It was observed that women eating with a male companion chose foods of significantly lower calorific value than when eating with another woman. The group size did not play a significant role; the calorie intake of women was negatively associated with the number of men in the group, whereas the number of women in the group showed a marginally significant positive impact. On the other hand, the total number of men or women did not affect the total calorie intake by men. In another study, where male and female subjects had snacks with same-sex and opposite-sex partners, female subjects ate significantly less in the presence of a desirable male partner presenting themselves as a “feminine light” [10]. In contrast, men did not eat more or less in the company of a desirable

woman. Moreover, it has been demonstrated that people tend to eat more in groups than alone [11]. Therefore, people look for cues from the environment to determine when to stop eating when palatable food is available, and satiety is no issue. Interestingly, it has also been documented that both males and females eat less in the presence of a stranger of the opposite sex than when a person of the same sex is present [12].

The social effects on dietary habits were revealed in a study on marital transitions in men [13]. In a study on 38,865 men assessed at four-year intervals (1986–90 and 1990–94), it was demonstrated that alcohol consumption increased in widowed men. Moreover, divorced or widowed men experienced a decreased body mass index (BMI), but at the same time a lower intake in vegetables. Social factors play an important role in dietary intake such as food availability in specific ethnic minority settings in American Indian reservations, Canadian First Nations reserves, the Marshall Islands, and inner-city Baltimore [14]. Important factors include proximity to food stores and costs. This reflects limited availability and promotion of healthy foods. Therefore, it is important to pay special attention to support food environments in low-income ethnic subpopulations. Another social aspect relates to the ability of consumers to understand the information on nutrition labels [15]. In a total of 17 studies – nine randomized and eight cohort studies – school-age children, older adults, and diabetes patients were subjected to a range of taught sessions and web-based education. Although some results obtained were heterogenous, a statistically significant improvement in understanding or use of nutrition labels was observed in all studies.

2.1.3. Ethnic Aspects of Nutrition

The importance of ethnicity should not be overlooked when discussing the habits of dietary intake. For instance, child obesity has shown higher prevalence by race, ethnicity, and socioeconomic status [16]. Factors contributing to increased child obesity in low-income and minority children relates to children watching more television thereby being exposed to more commercials advertising high-calorie, low-nutrient food. Moreover, poor neighborhoods accommodate more fast-food restaurants and fewer vendors of healthy foods. Children in low-income families were also exposed to reduced physical activity due to unsafe streets and lack of appropriate playground facilities. For this reason, schools are in a prime position to support effective obesity prevention. Moreover, existing policy levers can be used to reach ethnic minority and low-income children and families, but further changes in social and physical environments are needed.

In another approach, 2502 middle-school children in Texas were subjected to a study on racial and ethnic differences related to healthy and unhealthy eating in a home food environment, targeting obesity and obesogenic behaviors [17]. The study revealed that white children had a significantly better home food environment with superior access to healthy food than Hispanic and black children. Ethnicity has also played an important role in disease prevalence, showing lower risk of nutrition-related diseases [18]. In this context, there are fewer heart disease and cancer deaths among Caribbean-born migrants in the United Kingdom compared to the general population, probably due to different dietary habits including higher consumption of fruits and vegetables, and lower intake of fat. Follow-up studies in second-generation offspring adapted to British dietary habits with increased fat and reduced vegetable and fruit consumption should provide further insight into the effect of nutrition on disease development. In another study, the relationship between ethnicity and nutrition was studied in 9-to-14-year-old girls in Hawaii [19]. A comparison of nutrient and food group intakes in Asian girls, girls of mixed ethnicity, and white girls with physical activity levels, measurement of height, weight, BMI, and skinfold thickness suggested ethnic differences. For instance, Asian girls showed lower fiber, iron, folate, and calcium intake, whereas mixed ethnicity girls had the highest sweetened carbonated beverage intake. Overall, the outcome of the study indicated that intake of grain, vegetable, and fruit should be encouraged to support a balanced diet for adolescent girls in Hawaii. Moreover, serum 25-hydroxyvitamin D levels were measured in 6228 individuals to determine the association with diabetes in different ethnic groups [20]. The outcome of the study revealed an inverse association between vitamin D status and diabetes in non-Hispanic whites and Mexican Americans. However, this association could not be established in non-Hispanic blacks, which may be related to decreased sensitivity to vitamin D.

Finally, ethnicity plays an important role in nutritional risk and social isolation [21]. A study of 1000 community-dwelling older adults (65 or older) showed that black women were at greatest nutritional risk. The nutritional risk was associated with both lack of transport and low income. Moreover, black men as well as women were more likely to be socially isolated in comparison to their white counterparts. Individuals within the group of white men who were not married or did not attend religious services showed increased nutritional risk.

2.2. Nutrition and Disease Risk

Numerous studies have indicated that nutrition plays a highly important role in the development of various diseases such as cancer, cardiovascular disease, birth defects and cataracts [22]. Although not conclusive, there is plenty of evidence that nutrition rich in vegetables and fruits has contributed to a lower risk of disease development. For this reason, various dietary guidelines have been introduced [23]. As the US Department of Agriculture Healthy Eating Index (HEI) resulted in only a small reduction in major chronic disease risk, alternative measures of diet quality were implemented to be more effective. In this context, the Alternate Healthy Eating Index (AHEI) was associated with significant reduction in risk of major diseases in both men and women. In comparison, the recommended food score (RFS) was less efficient in predicting disease risk.

More specifically, certain naturally occurring pigments such as carotenoids in plants, microalgae, bacteria, and fungi have been demonstrated to affect human health [24]. Consumption of carotenoids has been associated with reduced risk of cancer, cardiovascular, and eye diseases. Similarly, other nutritive bioactive compounds of food and beverages such as phenolic acids, flavonoids, coumarins, alkaloids and other compounds play an important role in reducing the risk of noncommunicable diseases [25]. In this context, various biological effects including antioxidant, antibacterial, antiviral, anti-inflammatory, antiallergenic, antithrombotic, and vasodilatory actions have been related to bioactive compounds. Moreover, food groups and intermediate disease markers have been identified by network meta-analysis, covering a total of 66 randomized trials comparing 10 food groups [26]. In the context of reduction of low-density lipoprotein (LDL) cholesterol, nuts were superior (93%) followed by legumes (85%) and whole grains (70%). Moreover, fish (97%) was best for triglycerol reduction, followed by nuts (78%) and red meat (72%). Therefore, increased intake of nuts, legumes, and whole grains turned out to be more efficient in improving metabolic health than any other food group evaluated. Obviously, nutrition can also have a negative impact on human health and thereby may promote disease development. For instance, several studies have suggested that red meat consumption might increase the risk of disease; red meat intake has been associated with various diseases including colorectal and other types of cancers, atherosclerotic and cardiovascular diseases, type 2 diabetes, and inflammatory processes [27]. Several theories have been proposed including red-meat-associated agents, saturated fat, and high salt intake. Possible mechanisms, however, not specific for red meat relate to trimethylamine N-oxide generation by microbiota, contamination

by environmental pollutants, and polycyclic aromatic carcinogens. The impact of N-nitroso compounds, heme iron, and catalyzation of endogenous nitrosation by heme should not be discarded. However, as heme is denatured by cooking, plasma hemopexin blocks its tissue delivery, allowing contribution to colorectal cancer development locally. More recent hypotheses indicate that infectious agents in beef might contribute to colorectal cancer development and metabolic incorporation of a nonhuman sialic acid – N-glycolylneuraminic acid – into the tissues of red meat consumers, which might trigger disease development. Interestingly, consumption of red meat has not been linked to high risk of disease in other carnivores. Below, examples of the effect of nutrition on specific disease groups are presented.

2.2.1. Nutrition and Cancer

The suggestion that dietary issues are responsible for the risk of one-third of cancers in the US has been discussed already in the 1980s [28]. Likewise, the World Cancer Research Fund/American Institute of Cancer Research has stated that related to global cancer development, nutrition plays an essential role [29]. Recently, it has been estimated that two-thirds of cancer-related deaths are preventable by significant modifications of dietary intake and lifestyle [30]. There are many causes of cancer including genetic components involving proto-oncogenes, many of which have been identified [31]. Activation of oncogenes is postulated to be related to mutations leading to uncontrolled cell division. However, it is thought that a single mutation is insufficient to trigger cancer development as multiple mutations are found in human cancers [32]. To further complicate the situation, there are reports indicating that epigenetic modifications can result in cancer development [33]. For instance, altered DNA methylation has been associated with cancer [34]. Moreover, epigenetic alterations have been demonstrated to be induced by dietary and environmental factors [35]. In this context, environmental exposures including diet, tobacco, alcohol, physical activity, stress, carcinogens, genetic factors, and infectious agents have been shown to influence the three recognized epigenetic functions, which are DNA methylation, histone modifications, and microRNA (miRNA) expression. However, quite astonishingly, recent statements have claimed that nutritional epidemiology of cancer is dead [7]. These statements are incorrect as the associations between plant foods and cancer, fat and breast cancer, meat and cancer, Westernization of diet and lifestyle, and other factors have demonstrated. Examples of the link between nutrition and cancer are presented below and in Table 2.1.

There are numerous meta-analysis studies, which strongly support preventive and therapeutic benefits of dietary modifications in relation to various types of cancers [36, 37]. Related to brain cancer, a systematic review and meta-analysis of 18 published studies was triggered by some inconsistency in the relationship between red meat consumption and the risk of glioma development [38]. The outcome was a significant positive association between intake of unprocessed red meat and risk of glioma. Moreover, a meta-analysis of nine observational studies suggested that fish consumption might contribute to reduced risk of brain cancer although additional cohort studies are necessary to confirm this association [39]. In a meta-analysis study, two large cohorts with repeated dietary measures over time, the Nurses' Health Study and Health Professionals Follow-up Study, processed meat intake was positively associated with colorectal cancer risk, particularly distal cancer [40]. However, there was little evidence that higher intake of unprocessed meat increased the risk of colorectal cancer.

Table 2.1. Examples of association between nutrition and cancer.

Cancer	Nutrient/Source	Effect	Ref
Brain	Red meat	Association with increased glioma risk	[38]
	PUFAs in fish	Reduced brain tumor risk	[39]
	Ast, Dau, Pec isolated from plants	Neuroprotection in neuroblastoma cells	[43]
Breast	Fiber	Reduced risk of breast cancer	[44, 45]
	Dairy products (excluding milk)	Reduced risk of breast cancer	[37]
	Soy isoflavone (soybeans)	Reduced risk of breast cancer in Asians	[46]
	Fruit and vegetable consumption	Reduced risk of premenopausal cancer	[47]
	Vitamin D	Reduced risk of breast cancer	[48]
	Modern diet (less fruits, vegetables)	Increased risk of ER breast cancer	[49]
	Flavonoids	Association with reduced breast cancer risk	[64]
	Isoflavones	Association with reduced breast cancer risk	[64]
	Licoricidin	Metastasis inhibition in breast tumor model	[62]

Colon	Vegetables and fruits	Reduced risk of colon cancer	[50]
	Vegetables and fruits	Reduced risk of colon cancer	[52]
Colorectal	Coffee	Reduced risk of colorectal cancer	[55]
	Processed red meat	Increased risk of colorectal cancer	[40, 41]
Gastric	Flavonoids	Association with reduced colorectal cancer risk	[64]
Esophageal	Red meat, obesity	Association with reduced colorectal cancer risk	[27]
Stomach	Processed red meat	Association with increased gastric cancer risk	[41]
	Aged garlic extract	NK cell stimulation	[73]
	Isoflavones	Association with reduced colorectal cancer risk	[64]
	Catechins, theanine	Reduced risk of esophageal cancer	[51]
	Spices (ginger, garlic, pepper, etc.)	Prevention, therapeutic effect on cancers	[53]
Prostate	Green tea extracts	Reduced tumor volume in mice	[58]
	Green tea, polyphenol EGCG	Reduced risk of cancer	[59]
	Nigerian diet (fruits, herbs, spices)	Potential reduction in cancer risk	[60]
	Broccoli sprouts	Reduced prostate cancer incidence	[61]
	Eggs	Association with cancer cannot be ruled out	[67]
	Licoricidin	Anti-cancer activity	[62]
Ovarian	Dietary acrylamide	Cause of ovarian cancer	[63]
	Isoflavones	Association with decreased ovarian cancer risk	[64]
	Fiber intake	Reduced risk of ovarian cancer	[66]
	Eggs	Association with cancer cannot be ruled out	[67]
Endometrial	High sugar intake	Inverse risk of ovarian cancer	[66]
	Coffee	Inverse association with endometrial cancer	[56, 57]

Liver	Coffee	Decreased risk of liver cancer	[55]
	AUR in citrus fruit	Inhibition of hepato-carcinogenesis in rats	[69]
	Deproteinized asparagus polysaccharide	Anticancer activity in vitro and in vivo	[70]
	Celery seeds	Protection against hepatocarcinogenesis	[71]
	Aged garlic extract	NK cell stimulation	[73]
Lung	Flavonoids	Association with decreased lung cancer risk	[64]
	Cruciferous vegetables	Reduced risk of lung cancer in non-smokers	[74]
	Vitamin E	Protective effect against lung cancer	[75]
	Grape seeds	Decreased proliferation of malignant cells	[76]
Pancreatic	Aged garlic extract	NK cell stimulation	[73]
	Folate (vegetables, fruits)	Reduced risk of pancreatic cancer	[78]
	Alcohol	Heavy drinking, high pancreatic cancer risk	[79]
	β-carotene, zeaxanthin, α-tocopherol	Inverse association with pancreatic cancer risk	[80]
Skin	Proanthocyanidines (grape seeds)	Anti-skin cancer activity	[82]
	Anthocyanidins (grape seeds)	Reduced growth of non-melanoma tumors	[85]
	Folate	Sun protection, reduced skin cancer risk	[83]
	Reduced Vitamin D, 25(OH)D level	Reduced survival of melanoma patients	[84]
	Vitamin D and VDR	Inverse relation to melanoma progression	[84]
Thyroid	Coffee, tea	No association with thyroid cancer risk	[86]

Ast, astragalin; AUR, auraptene; EGCG, epigallocatechin gallate; ER. Estrogen-receptor negative; Dau, daucosterol; NK cell, natural killer cell; Pec, pectolinarin; PUFAs, poly-unsaturated fatty acids; VDR, vitamin D receptor.

According to another meta-analysis based on 42 eligible studies, no association between intake of red and processed meat, and gastric cancer was observed in cohort studies, although case-control studies resulted in a positive association [41]. Moreover, a study conducted in Kuwait demonstrated that obesity, excessive red meat intake and infrequent fruit

and vegetable consumption resulted in increased risk of colorectal cancer [42].

In another approach, daucosterol (Dau), pectolinarin (Pec), and astragalin (Ast), plant components from *Cirsium setidens* and *Aster scaber*, were verified for neuroprotection in human neuroblastoma SK-N-SH cells [43]. Indeed, ethyl acetate fractions from *C. setidens* and *A. scaber* provided neuroprotection by downregulation of MAPK pathways, generally associated with cancer development, and upregulation of several antioxidant genes. In the case of breast cancer, fiber intake has been demonstrated to reduce the risk of disease [44, 45]. In these studies, a significant inverse dose–response link was observed between fiber consumption and risk of breast cancer. Moreover, another study including over one million participants indicated a reduced risk of breast cancer after consumption of dairy products excluding milk [37]. Breast cancer was investigated in a meta-analysis of four trials on breast cancer reoccurrence and 14 studies on breast cancer incidence, which indicated that soy isoflavone intake from soybeans was associated with a significant reduction in breast cancer risk in Asian women [46]. The effect of fruit and vegetable consumption was evaluated in 90,476 premenopausal women in the United States, which demonstrated that total fruit consumption during adolescence was associated with a lower risk of breast cancer [47]. High intake of fruits and vegetables rich in α-carotene in early adulthood was linked to reduced risk of premenopausal breast cancer. Moreover, consumption of greater quantities of apple, banana, and grapes during adolescence, and oranges and kale during adulthood resulted in significantly reduced breast cancer risk. In another study, the effect of vitamin D intake on breast cancer risk was evaluated in women in Iran [48]. Based on food frequency questionnaires and serum measurements of 25-hydroxyvitamin D (25(OH)D) in blood, women with high intake of vitamin D had a three times lower risk of developing breast cancer. It was also demonstrated that women consuming modern diets consisting of more grains, dairy products, and sugar, but fewer fruits and vegetables, showed lower tissue omega-3 fatty acids and higher omega-6 and trans fatty acids, and were associated with enhanced risk of estrogen receptor-negative breast cancer [49].

In the context of gastric and esophageal cancers, the European Prospective Investigation of Cancer and Nutrition (EPIC) study showed a statistically significant inverse association between nutrition and the risk of esophageal squamous cell carcinoma [50]. Furthermore, catechins and theanine, the main active ingredients of green tea, have been linked to reduced risk of colon and esophageal cancers [51]. In another study, the risk of proximal

colon, distal colon and rectal cancers was evaluated in Western Australia in relation to fruit and vegetable consumption [52]. The results indicated no association between total fruit and vegetable intake and proximal colon or rectal cancer. In contrast, intake of brassica vegetables inversely correlated with proximal colon cancer. Moreover, negative trends were observed for distal colon cancer after total fruit and vegetable intake. The risk for distal colon cancer was significantly decreased after consumption of dark yellow vegetables and apples. However, an increased risk of colorectal cancer was linked to fruit juice intake. Spices such as *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 also been suggested for prevention and treatment of several cancers including colorectal and stomach cancers [53]. The bioactive compounds such as curcumin, thymoquinone, piperine and capsaicin found in these spices can contribute to induction of apoptosis, inhibition of proliferation, migration and invasion of tumors, and sensitization of tumors to radiotherapy and chemotherapy.

Coffee represents an interesting dietary component, and has been evaluated for its association with the risk of various cancers. In this context, coffee has been suggested to decrease the risk of colorectal cancer [54]. Further analysis of the effect of coffee, decaffeinated coffee, and caffeine in rats demonstrated that only coffee decreased the development of dysplastic crypts after exposure to the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). On the other hand, only decaffeinated coffee increased the number of metallothionein-positive crypts, while coffee and caffeine inhibited cyclooxygenase-2 (COX-2) in the colon. Coffee might therefore contain other compounds with greater chemoprotective effects than caffeine. Epidemiological evidence has indicated that coffee protects against liver and colorectal cancers [55]. In contrast, coffee intake showed no association with a reduced risk of breast and prostate cancers. However, inverse association with coffee intake was detected in postmenopausal breast cancer patients, and in advanced breast and prostate cancer survivors. Moreover, meta-analysis studies have shown an inverse relation between endometrial cancer risk and coffee consumption [56, 57].

Related to prostate cancer, green tea extracts were demonstrated to support a significant reduction in tumor volume and tumor size in severe combined immunodeficiency (SCID) mice bearing human LAPC4 prostate tumors after addition of brewed green tea to the drinking water [58]. Moreover, the anticarcinogenic effect of the polyphenol epigallocatechin gallate (EGCG) found in green tea was evaluated in Chinese men in Hong Kong who were

consuming green tea [59]. The study showed that the cancer risk was inversely associated with green tea consumption and intake of EGCG. Local plants including the African bush pear (*Dacryodes edulis*), horseradish tree (*Moringa oleifera*) and clove (*Syzygium aromaticum*) provide fruits, herbs and spices for Nigerian food ingredients containing polyphenols (EGCG, methylgallate, kaempferol, and quercetin) [60]. Additionally, the Nigerian diet contains other components of interest such as soybeans (isoflavones), chili pepper (capsaicin), and green tea (epicatechin). Overall, modifications of dietary intake in the direction toward antioxidants and chemopreventive agents should support prevention of prostate cancer, especially in Africa where there is high prevalence of the disease. Cruciferous vegetables including broccoli sprouts have been associated with chemoprevention of cancer due to their content of sulforaphane (SFN) [61]. In the context of prostate cancer, mice fed on broccoli sprouts showed the presence of SFN metabolites in liver, kidney, colon, and prostate tissues, which reduced prostate cancer incidence and the progression of invasive cancer. In another study, licorice extracts demonstrating anticarcinogenic activity have been verified in tumor cell lines [62]. In this context, a hexane/ethanol extract of *Glycyrrhiza uralensis* (HEGU) containing the active compound licoricidin induced apoptosis and G1 cell cycle arrest in human prostate DU145 cells as well as inhibited metastasis in the 4T1 breast cancer model.

In the case of ovarian cancer, epidemiological studies have focused on the association with dietary acrylamide intake [63]. In the prospective Netherlands Cohort Study (NLCS) of 62,573 women, no statistically significant interaction between dietary acrylamide intake and gene variants including 57 single-nucleotide polymorphisms (SNPs) and two gene deletions was revealed. However, regarding SNPs in the HSD3B1/B2 gene cluster, nominal statistically significant interactions with dietary acrylamide intake was confirmed, suggesting that action through sex hormones caused ovarian cancer. In a meta-analysis of 143 studies, the association between isoflavones and decreased risk of ovarian cancer was confirmed [64]. Moreover, the analysis revealed an association between flavonoids and decreased risk of colorectal cancer [64]. However, another meta-analysis covering 220 publications containing prospective and case-control studies on quercetin, a flavonoid, provided no significant association with a decrease in ovarian cancer [65]. A study of African American women revealed an inverse association between fiber intake and the risk of ovarian cancer [66]. Moreover, higher glycemic load and high intake of total sugars were associated with increased risk of ovarian cancer. In a dose–response meta-analysis study, the relationship between egg consumption and the risk of breast, prostate, and ovarian cancer was evaluated [67]. Although there

was a non-significantly enhanced risk for breast cancer after an increase in consumption of five eggs per week, a positive association between egg intake and fatal prostate and ovarian cancers could not be excluded.

The prevention and treatment of liver cancer have included natural dietary products such as grapes, black currants, plums, pomegranates, cruciferous vegetables, French beans, tomatoes, asparagus, garlic, turmeric, ginger, soy, rice bran, and some edible fungi [68]. For instance, auraptene (AUR), an antioxidant agent isolated from citrus fruits, effectively inhibited chemically induced hepatocarcinogenesis in a rat model [69]. Furthermore, AUR exposure suppressed beta-catenin mutations in N-nitrosodiethylamine-induced hepatocellular carcinomas in rats. In another study, the anticancer effect of deproteinized asparagus polysaccharide was demonstrated in vitro in hepatocellular carcinoma Hep3B and HepG2 cells and in vivo [70]. Moreover, celery seeds protected against experimentally induced hepatocarcinogenesis in Wistar rats [71]. Furthermore, garlic extracts have been demonstrated to induce a p53/p21-dependent cell cycle arrest in the G2/M phase and apoptosis leading to inhibition of transformed hepatoma cells in vitro [72]. The immunomodulative and antioxidative effects of aged garlic extract were evaluated in 50 patients with inoperable colorectal, liver, or pancreatic cancers [73]. The number of natural killer (NK) cells and the NK cell activity increased in patients treated with aged garlic extract in comparison to the placebo group, although no difference in quality of life was observed.

Concerning lung cancer, a study involving 82,330 individuals with no previous history of lung cancer was conducted in Japan for the association between cruciferous vegetables rich in isothiocyanates and lung cancer [74]. After almost 15 years, 1499 participants were diagnosed with lung cancer, but no significant inverse association between vegetable intake and risk of lung cancer was observed. However, including smoking as a factor in the study revealed that a significant inverse association between vegetable consumption and lung cancer risk was established in nonsmokers. In a meta-analysis study on vitamin E consumption and lung cancer risk it was suggested that for every 2 mg/day increase in dietary vitamin E intake, the risk of lung cancer decreased statistically by 5%, indicating that vitamin E can provide a protective effect [75]. Furthermore, grape seed procyanidin extract significantly reduced the proliferation of lung premalignant and malignant cells [76]. Finally, a meta-analysis comprising 10 studies including 5085 patients was conducted to clarify the impact of the prognostic nutritional index (PNI) in lung cancer prognosis [77]. Clearly, a low PNI showed a correlation with unfavorable overall survival, especially

related to non-small-cell lung cancer patients, thereby serving as a novel biomarker in clinical practice.

The depressingly poor five-year pancreatic cancer survival rate of only 6% has triggered serious preventive and therapeutic research activities including nutritional aspects [78]. In this context, consumption of vegetables and fruits containing folate has demonstrated a reduced risk of pancreatic cancer, while a diet rich in red meat and saturated fat increased the risk. In a meta-analysis based on 32 published studies, a reduced risk of pancreatic cancer was shown for the highest category of healthy pattern in comparison to the category of the lowest healthy pattern and heavy drinking [79]. Overall, healthy and light–moderate drinking patterns may decrease the risk of pancreatic cancer, whereas Western-type and heavy drinking patterns may enhance the risk. The association between carotenoids, vitamin C, retinol (vitamin A1), and tocopherols (vitamin E) and the risk of pancreatic cancer was evaluated in 446 exocrine pancreatic cancer patients and 446 controls within the EPIC study [80]. Higher plasma concentrations of β-carotene, zeaxanthin, and α-tocopherol showed an inverse association with the risk of pancreatic cancer. However, the EPIC study involving more than half a million participants from 10 European countries indicated that there was no association between an alcohol-free Mediterranean diet and reduced risk of pancreatic cancer [81].

The occurrence of skin cancer has dramatically increased due to frequent exposure to UV light, now reaching an incidence equivalent to cancers in all other organs combined [82]. Dietary phytochemicals such as grape seed proanthocyanidins (GSPs) have been demonstrated to provide anticancer activity by significantly inhibiting UV radiation-induced skin tumor development in animal models [82]. The GSP action is based on inhibition of inflammation, DNA repair, and stimulation of the immune system. Furthermore, large-scale epidemiological and nutritional studies have suggested a link between folate intake and reduced risk of cancer due to its role in DNA repair and replication [83]. Folate has been indicated to play an important role in skin cancer and to potentially protect the skin from exposure to the sun, and thereby folate intake and topical delivery may provide a strategy for cancer prevention [83]. Vitamin D3 has been associated with anticarcinogenic and anti-melanoma activity in experimental models [84]. These activities are mediated by vitamin D receptors (VDRs) or retinoic acid orphan receptors (ROR)-α or ROR-γ. Low levels of hydroxylated vitamin D (25(OH)D) are associated with reduced survival of melanoma patients. Moreover, an inverse correlation was established between ROR-α and ROR-γ expression and progression of

melanoma [84]. Related to nonmelanoma skin cancer, it was demonstrated in a radiation-induced mouse model that dietary supplementation of GSPs showed anticarcinogenic activity and significantly inhibited the growth and multiplicity of skin tumors [85]. The dietary supplementation promoted repair of damaged DNA, which further stimulated the immune system through activation of dendritic cells.

Finally, as both coffee and tea have demonstrated anticarcinogenic activity in cellular and animal studies for several cancer indications, it triggered the investigation of coffee and tea intake involving 476,108 adult men and women in the EPIC study in relation to thyroid cancer [86]. The 14-year follow-up study indicated no association between coffee and tea consumption and the risk of thyroid cancer.

2.2.2. Nutrition and Metabolic Diseases

The effect of nutrition on metabolic disease has been documented through several studies, of which some examples are presented below and in Table 2.2. In this context, as weight problems and obesity has doubled since 1980, it affects nearly one-third of the world population and thereby presents a serious risk not only to metabolic diseases, but also other indications such as enhanced prevalence of cancer and cardiovascular disease [87]. Related to type 2 diabetes, in the population-based Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) the association of egg consumption and disease was investigated in middle-aged Finnish men [88]. The study showed different serum profiles for subjects with high intake (one egg/day) or low intake (two eggs/week) of eggs compared to those who developed type 2 diabetes or remained healthy. A negative correlation between certain metabolites and high egg intake, and a positive association with low egg intake were observed. The increase in type 2 diabetes in Asian populations has been suggested to be associated with increased rice intake. However, the 11-year follow-up of the Singapore Chinese Health Study on 45,411 male and female participants indicated no link between rice intake and higher risk of type 2 diabetes [89]. Replacement of one daily serving of rice with noodles, red meat, or poultry was associated with higher risk of type 2 diabetes, whereas replacements with white bread or whole wheat bread lowered the risk [89]. Related to the health benefits of the Mediterranean diet associated with the intake of large quantities of vegetables, the role of red meat has been overlooked [90]. Although existing guidelines recommend limited intake of red meat, there is not enough scientific evidence to suggest a strict limitation in the general population, although there is substantial evidence to propose elimination of the intake of

processed meat from the diet. The effect of coffee consumption on the risk of type 2 diabetes was studied in the Shanghai High-Risk Diabetic Screen (SHiDS) demonstrating lower plasma glucose levels and higher insulin levels at fasting after adjustment for age, fat percentage, BMI, waist circumference, tea and alcohol intake, smoking habits, family history of diabetes, and educational status [91]. The study showed that coffee intake was independently and positively related to pancreatic β-cell function in a large high-risk diabetic Chinese population.

Consumption of a high-fat diet has been identified as a significant modifiable risk factor for diseases such as diabetes [92]. Exposure to a high-fat diet can trigger insulin resistance and dysfunction of pancreatic β cells as demonstrated in mice, which developed systemic insulin resistance and glucose intolerance after only three days of high-fat diet intake [93]. The causative and correlative association between inflammation induced by the intake of a high-fat diet and the pathogenesis of insulin resistance has been established, although further studies are needed to confirm it [94]. Overall, overconsumption of a high-fat diet can be mechanistically linked to the development of insulin resistance and type 2 diabetes.

The association between sugar-sweetened soda consumption and diabetes was evaluated in the Northern Manhattan Study involving 2019 participants [95]. The study demonstrated that intake of sugar-sweetened soda was positively associated with diabetes, which was largely explained by the BMI, although the association remained strong and independent of BMI in overweight and obese individuals. However, despite the link from consumption of sugar-sweetened beverages being undisputable, switching to artificially sweetened diet beverages may not reduce the risk of diabetes.

Table 2.2. Examples of association between nutrition and various diseases.

Disease	Nutrient/Source	Effect	Ref
Diabetes	Egg consumption	Reduced risk of diabetes	[88]
	Rice	No link between rice and diabetes risk	[89]
	Red meat	Replacement of rice, increased diabetes risk	[89]
	Mediterranean diet including meat	Reduced risk when processed meat eliminated	[90]
	Coffee	Association with pancreatic β cell function	[91]
	High fat diet	Increased risk of diabetes	[92]
	PUFAs	Prevention/lower risk of diabetes	[98]
	Red meat reduction	Reduced risk of diabetes	[103]
	Sugar-sweetened beverages	Increased risk of diabetes	[95]
Cardiovascular	PUFAs	Reduced risk of cardiovascular disease	[98]
	Peanuts, tree nuts, walnuts	Lower risk of heart & cardiovascular diseases	[99]
	Red meat replaced by fish	Reduced risk of ischemic stroke	[100]
	Red meat	Higher risk of cardiovascular disease	[101]
	Fruits and vegetables	Lower risk of stroke, ischemic heart disease	[102]
	Red meat reduction	Reduced risk of cardiovascular disease	[103]
	Coffee	Reduced risk of hypertension	[104]
	Chocolate	Reduced risk of myocardial infarction, stroke	[105]
Infections	Micronutrient deficiency	Higher risk of infection	[106]
	Vitamin A	Reduced severity of diarrhea, lower mortality	[107]
	Zinc	Reduced duration and severity of diarrhea	[107]
	Micronutrients	Positive effect on pneumonia and malaria	[107]
		Association with infection, clinical outcome	[108]