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Epigenetics: Diet and Cancer

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Abstract

Epigenetic modifications including DNA methylation, histone modifications and RNA interference (RNAi) provide a significant impact on human health and disease development. Changes in epigenetic functions result in disturbance in gene regulation and aberrant gene expression, which strongly contributes to progression of various types of cancers. The reversible nature of epigenetic functions has made them attractive as targets for drug development. In this context, DNA methyltransferase inhibitors and histone deacetylase inhibitors have been targeted against cancers. RNAi, specifically microRNAs (miRNAs) have demonstrated differential expression including up-regulation and down-regulation in a number of cancers. Furthermore, miRNA levels in biofluids (serum and urine) provide opportunities for diagnostic applications of epigenetics. Nutrition has been demonstrated to have a substantial impact on epigenetic mechanisms. Dramatic changes in dietary intake have been shown to affect epigenetic functions and might provide the means for a significant reduction in cancer risk and also may contribute to disease prevention. Furthermore, revision of diet in cancer patients has resulted in changes in gene expression, which can enhance therapeutic efficacy. Especially, diets rich in fruits, vegetables, fish and fibers and reduction in consummation of red meat have influenced the epigenome and thereby provide both prophylactic and therapeutic efficacy.

Keywords: Epigenetics; Nutrition; Cancer; DNA methylation; Histone modifications; Micro RNA

Introduction

Although a number of genetic variations such as point mutations [1], deletions [2], insertions [3] and copy number variations [4] have been identified to affect gene expression, fairly recent findings have also demonstrated the involvement of epigenetic mechanisms showing significant impact on disease development [5]. As epigenetic modifications do not involve changes in the primary DNA sequence they are reversible and therefore potentially attractive as targets for drug discovery and development. Epigenetic changes consist of DNA methylations [6], histone modifications [5] and RNA interference (RNAi) [7]. DNA methylations have been linked to both up- and down-regulation of mRNA transcription [8]. Related to histone modifications, particularly histones H3 and H4 are modified by acetylation, methylation, ubiquitination and phosphorylation [9], which can lead to both up- and down-regulation of transcription [10,11]. Moreover, the phenomenon of RNAi involves 21-23 nucleotide long single-stranded microRNAs (miRNAs), which by interfering with mRNA leads to down-regulation of gene expression [12,13]. More than 1800 miRNAs are deposited in databases [14] and a large number of miRNAs have been associated with different diseases [12,15] as described in more detail below.

In this review, emphasis will be placed on the association of abnormal epigenetic modifications to the promotion of cancer development. As more and more discoveries are made in this area it will only be possible to illustrate the progress through selected examples involving DNA methylation, histone modifications and RNAi. Additionally, the effect of food intake and its effect on epigenetic mechanisms leading to disease will be discussed. Most importantly, substantial dietary changes have demonstrated a profound effect on epigenetic functions and might therefore provide both prophylactic and therapeutic efficacy against cancer and other diseases.

Epigenetics and Cancer

Related to epigenetics, it has been discovered that dietary factors play an important role. In this context, bioactive food compounds such as folate, polyphenols, selenium and retinoids demonstrate a strong impact on DNA methylation and histone modifications [16]. Furthermore, nutritional modifications have been identified to be responsible for aberrant miRNA expression [17]. Cancer provides next to cardiovascular diseases the highest mortality worldwide. The development of cancer is postulated to be a multi-step process and until recently was considered to rely on mutations in crucial genes [18]. Intensive research has revealed the involvement of epigenetic mechanisms responsible for breakdown in gene regulation. In this context, DNA methylation, histone modifications and RNAi have all been revealed to contribute to cancer development.

DNA Methylation

In epigenetic modulations based on DNA methylations a methyl group (CH_3) is covalently added to the 5'-position of cytosine upstream of guanosine affecting the regulation of gene expression, which presents an impact on differentiation, genomic imprinting and DNA repair [6]. The methylated CpG islands are clustered prominently in the promoter regions of genes and can result in reduction, cessation or up-regulation of mRNA transcription, which has been associated with cancer [19,20]. For instance, inactivation of tumor suppression genes such as *HIC1, INK4b* and *TIMP3* has been

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associated with hypermethylation in their promoter regions [21]. DNA hypermethylation of the *SPRY2, RASSF1A, RSK4, CHFR* and *CDH1* genes has been linked to endometrial cancer [22]. In breast cancer, DNA methylation has been indicated to play an important role demonstrated by altered methylation of several genes in cancer tissue [23]. Furthermore, heterogeneity in transcription activity and differential metastatic behavior were observed in DNA methylome analysis of primary breast cancer [24]. Divergent changes primarily in CpG island-poor regions were discovered after profiling the DNA methylome and transcriptome of 44 matched primary breast tumors and regional metastasis. Altered DNA methylation patterns have also been observed in prostate [25] and rectal [26] cancer patients. It has been established that *Helicobacter pylori* infection can induce DNA methylation, which might be associated with gastric cancer risk. A cross-sectional study of 281 Japanese individuals revealed that mean methylation levels were 2.5-34.1 times higher in the presence of *H. pylori* infections [27]. Furthermore, in presence of *H. pylori* infection the miR-124a-3 methylation levels were increased in smokers and reduced in individuals consuming green/yellow vegetables. In contrast, these associations were not found in uninfected individuals.

Physical activity has also been linked to DNA methylation and disease [8]. For instance, in a study on more than 600 non-Hispanic white women with a family history of breast cancer, those that were involved in physical exercise showed a significantly higher LINE-1 methylation (which is an index of global DNA methylation) [28]. In another approach, the correlation between physical activity and DNA methylation was studied in 509 individuals aged 70 years and older using the Luminometric Methylation Assay (LUMA) [29]. Global methylation correlated with physical exercise. In contrast, in the Commuting Mode and Response Study physical activity was not associated with LINE-1 methylation [30].

In the context of DNA methylation, several drugs have been developed based on DNA Methyltransferase (DNMT) inhibitors. For instance, azacytidine and decitabine have been shown to be efficient epigenetic modulators [31,32]. However, toxicity and limited chemical stability have restricted applications for cancer therapy, which might be readdressed by using the more stable and less cytotoxic cytidine analogue zebularine (1-(β-dribofuranosyl)-1,2-dihydropyrimidin-2-one). DNMT inhibitors have also been combined with other drugs for cancer treatment. For instance, Esophageal Squamous Cell Carcinoma (ESCC) and Esophageal Adenocarcinoma (EAC) cells treated with azacytidine and Histone Deacetylase (HDAC) inhibitors targeted esophageal cancer cells by inducing DNA damage, cell viability loss and apoptosis [33]. Another example of DNMT and HDAC inhibitor combination relates to hydralazine-valporate treatment for cutaneous T-cell lymphoma [34]. The oral administration was proven safe, but further clinical trials need to be conducted to confirm the efficacy in other types of cancer.

Histone Modifications

Epigenetic functions also include histones, which play important roles in packaging DNA in chromatin structures [5]. Acetylation, methylation, ubiquitination and phosphorylation are the main modifications of histones H3 and H4 [9]. Histone acetylation has generally been associated with gene activation and decondensation [31] including activation of transcription [32] resulting in altered expression of oncogenes, tumor suppressor genes and DNA repair genes. For instance, histone H4 lysine 20 acetylation was enriched around transcription start sites of minimally expressed genes and in the gene body of over expressed genes indicating the association of a unique acetylation and gene expression [31]. In the context of colon cancer, histone H3 lysine 27 acetylation was up-regulated in esophageal cancer cells [33]. Epigenomic-based therapeutic approaches have also been applied for ovarian cancer targeting histone modifications and histone regulating enzymes [34]. In another study, a novel class I HDAC inhibitor MPT0G030 has showed induced cell apoptosis and differentiation in human colorectal cancer cells [35]. This *in vivo* anti-cancer activity suggests a great potential for cancer therapy. Furthermore, HDAC inhibitors have been applied for treatment of Non-Hodgkin's lymphoma [36]. At least four HDAC inhibitors (vorinostat, romidepsin, belinostat and panobinostat) have been approved by the FDA for cancer treatment [37]. Vorinostat is used for the treatment of cutaneous T-cell lymphoma [38] and combination therapies of vorinostat for various solid tumors are in progress. Moreover, several other HDAC inhibitors are currently subjected to clinical trials.

RNA Interference

RNAi has been strongly associated with the development of epigenetic drugs, especially in cancer therapy. In this context, it was demonstrated that miRNA-135b is up-regulated in sporadic and inflammatory bowel disease-associated human Colorectal Cancer (CRC) [39]. Increase in miRNA-135b levels correlated with tumor stage and poor clinical outcome. When over expressed miRNA-135b was inhibited the tumor growth was reduced by controlling downstream genes involved in proliferation, invasion and apoptosis in a CRC mouse model. In another study, miR-21, miR-126 and miR-143 dysregulation was associated with cervical cancer, which has attracted both therapeutic and diagnostic applications [40]. Moreover, altered expression of miR-15 and miR-16 has been detected in B-cell Chronic Lymphocytic Leukemia (CLL) [41] and miR-17-92 has been linked to B cell lymphoma [42]. Differential expression of miR-145 has been associated with breast [43], ovarian [44] and colorectal [45] cancer. A number of other miRNAs such as miR-141 and miR-200 are up-regulated in ovarian cancers, while miR-125b, miR-140, miR-145 and miR-199 are down-regulated [44]. Links between miR-21, miR-17-92 and miR-34a and glioblastoma [46], lung cancer [47] and pancreatic cancer [48], respectively, have also been described. Moreover, miRNAs possess tumor suppressor activity and for instance miR-143 and miR-145 showed oncogenic activity and suppressed the anti-apoptotic Bcl-2 gene [49].

In addition to therapeutic applications, diagnostic approaches have involved determination of miRNA levels in serum and screening of aberrant hypermethylation of miRNAs [50]. Furthermore, miRNAs detected in extracellular vesicles in biofluids were validated in urine samples of prostate cancer patients [51]. It was demonstrated that miRNA isoforms (isomiRs) with 3' end modifications showed significant differences in prostate cancer patients compared to control individuals.

Diet and Cancer

Nutrition plays an important role on human health and development of disease and particularly in the case of various cancers.

Already in the 1980s it was estimated that diet accounted for about a third of the risk of developing cancer in the US [52]. Furthermore, the World Cancer Research Fund and American Institute of Cancer Research Report concluded based on thousands of publications that diet provides globally a significant contribution to cancer [53] and most likely two thirds of cancer-related deaths could be prevented by dietary and lifestyle modifications [54]. Numerous studies have indicated or confirmed the influence of nutrition on cancer prevention and therapy. The enormous progress in bioinformatics, genomics and proteomics has lead to the foundation of nutrigenomics for a better understanding of the relationship between nutrition and disease [55]. In the context of cancer, understanding of the relationship between nutrition and cancer has been compromised by the existence of different cancer types, level of aggressiveness and presence at different stages of life. Moreover, individual variations in food consumption, digestion, metabolism and diversity related to geography, ethnicity and sociology has complicated the identification of food components promoting health and preventing disease [56].

Nutrition and Different Cancers

Cancer prevention approaches have included investigations of biologically active compounds from plants [57]. Several studies have demonstrated the impact of cruciferous vegetables, green tea, and spices like curry and black pepper on epigenetic modifications in female cancers [58]. Moreover, indol-3-carbinol (I3C) derived from cruciferous vegetables has recently been identified as an essential component of the anti-proliferative activity on breast cancer cells by the tumor suppressor miR-34a [59]. Therefore, studies on phytochemical-dependent miRNA level changes and novel substances such as brusatol or artemisinin are of great importance. Furthermore, understanding whether these substances demonstrate synergistic or antagonistic activity provides improved potential for successful cancer therapy. In a mouse model of basal-like breast cancer, chronic obesity was evaluated as a breast cancer risk factor for induction of mammary gland epigenetic reprogramming and increase in mammary tumor growth [60]. Animals with MMTV-Wnt-1 mammary tumors fed on a Diet-Induced Obesity (DIO) regimen showed larger mean tumor volumes, increase in serum IL-6 levels, enhanced expression of pro-inflammatory genes in the mammary fat pad and amplified mammary DNA methylation profiles in comparison to control mice. However, weight normalization was not sufficient to reverse the effects of chronic obesity on epigenetic reprogramming and inflammatory signals. Moreover, the impact of dietary sugar on mammary gland tumor development was studied in mouse models [61]. Sucrose intake comparable to levels in Western diets resulted in enhanced tumor growth and metastasis in mice compared to animals fed on a non-sugar starch diet. The increase in breast cancer risk was linked to over expression of 12-Lipoxygenase (12-LOX) and its arachidonate metabolite 12-Hydroxy-5Z,8Z,10E,14Z-Eicosatetraenoic acid (12-HETE) [61]. As assessment for reduced breast cancer risk of fiber intake has been inconclusive, a meta-analysis including 712,195 patients was conducted [62]. The outcome indicated that there was no significant difference between geographical regions, length of follow-up or menopausal status, but the overall conclusion was that a significant inverse dose-response existed between dietary fiber intake and risk of breast cancer. Another meta-analysis study showed that increased consumption of total dairy food, excluding milk, may have impact on a reduced risk of breast cancer [63]. Similarly, a significant reduction in breast cancer incidence was observed for soy isoflavone intake in a meta-analysis of 4 studies on breast cancer recurrence and 14 studies on breast cancer incidence [64]. In another approach, positive findings suggested that optimization of the selenium concentration in the diet can lower the risk of breast and ovarian cancer in women with a BRCA1 mutation [65].

In another study, chemoprevention of disease was evaluated for epigenetic diets based on cruciferous vegetables [66]. Kale, cabbage, Brussels sprouts and broccoli contain Sulforaphane (SFN) and I3C, which have been demonstrated to act as HDAC and DNA methyltransferase inhibitors and to regulate miRNAs. Extra virgin olive oil has been associated with reduced cancer risk [67]. The effect of extra virgin olive oil and its phenolic compounds on gene expression was evaluated in human colon cancer (Caco-2) cells and *in vivo* in rats exposed to short- and long-term diet containing extra virgin olive oil [67] as endocannabinoid levels have been demonstrated to be altered in patients with colorectal cancer [68]. Exposure of Caco-2 cells to 100 ppm extra virgin olive oil, 50 μM phenol extracts or 50 μM hydroxytyrosol evoked selective and transient up-regulation of the *CNR1* gene, which encodes for type I Cannabinoid receptor (CB1). In contrast, none of the other major elements of the Endocannabinoid System (ECS) such as CB2, GPR55 and TRPV1 receptors were affected. In Caco-2 cells stimulation by phenol extracts and hydroxytyrosol inversely correlated with DNA methylation of the *CNR1* promoter. Similarly, a 4-fold increase in CB1 expression was observed in the colon of rats subjected to 10 days of dietary extra virgin olive oil supplementation. Furthermore, miR-23a and miR-301a known to be involved in the pathogenesis of colorectal cancer showed 50% decrease after administration of extra virgin olive oil.

The role of diet in prostate cancer has received much attention [69]. In addition to other factors, the link to epigenetics has been investigated. For instance, the phytoestrogen genistein can demethylate CpG islands in the *GSTP1* promoter region, which enhances protein expression [70]. It has also been documented that genestein enhances/restores the expression of tumor suppressors such as PTEN, p53, CYLD, p21WAF1/CIP1 and p16INK4a in prostate cancer cell lines, which is attributed to demethylation and acetylation of H3K9 residues [71] or to increased expression of histone acetyltransferases resulting in enrichment of acetylated H3 and H4 histones [72]. Moreover, histone acetylation is also enhanced by the flavone apigenin *in vitro* and after oral intake [73]. A marked reduction of histone deacetylase activity was observed *in vivo* with a significant impediment on prostate cancer tumor growth. In another approach, polyphenols such as resveratrol demonstrated anti-cancer activity and might provide potential for chemoprevention and therapy of prostate cancer [74]. Several studies have indicated an anti-cancer effect in tissue cultures. Moreover, epigenetic mechanisms are mediated through regulation of chromatin modifier Metastasis-Associated protein 1 (MTA1) and miRNAs. Analogs of resveratrol present better bioavailability and therefore provide improved pharmacological potency and superior anti-cancer efficacy. Another approach was to subject low-risk prostate cancer patients, which had not undergone surgery or received radiation or hormonal treatment to a modified diet and lifestyle change [75]. Monitoring of gene

expression profiles before and three months after the intervention showed up-regulation of 48 genes and down-regulation of 453 genes, of which the majority were involved in protein metabolism, intracellular traffic and phosphorylation.

The effect of nutritional intake has also been evaluated in relation to the risk of stomach cancer. In this context, a statistically significant inverse association was observed for consummation of vegetables and fruits and the risk of esophageal squamous cell carcinoma [76]. Furthermore, tea and particularly green tea, which contains high concentrations of anti-oxidants have been demonstrated to favorably contribute to the prevention of esophageal and colon cancers [77]. Consumption of vegetables and fruits was evaluated in a case-control study in Western Australia, which suggested that the risk of proximal colon and rectal cancers was not linked to the intake of total amount of vegetables and fruits [78]. However, intake of Brassica was inversely related to proximal colon cancer and the risk of distal colon cancer was significantly reduced after intake of yellow vegetables and apples. Furthermore, in the Dutch cohort study a significant inverse association was observed between consumption of raw vegetables and esophageal adenocarcinoma [79]. Similarly, reduced risk for gastric cardia adenocarcinoma was discovered after Brassica and citrus fruit intake.

Gut Microbiome

Interestingly, the diet and the gut microbiome play an important role in epigenetic modulation related to cancer and other diseases [80]. Production of metabolites which serve as cofactors and allosteric regulators of epigenetic functions present a strong link to dietary factors, physical activity and environmental toxins. Maternal and neonatal nutrition demonstrate a significant influence on the epigenome of the offspring as the food consumed modulates the composition of the gut microbiota [81]. For instance, in breast-fed infants the microbiota predominantly consists of Bifidobacteria and a large number of diverse microbiota develops after the introduction of solid food intake. In contrast, formula-fed infants carry a microbiota composed of a variety of genera including enterobacteria such as Streptococcus, Bacteroides, and Clostridium, as well as members of the genus Bifidobacterium. From the age of 2 years, the gut microbiota remains relatively constant although disease, surgical interventions, drugs and diet can substantially modify it. Proof of a link between bacterial predominance and epigenetic profile was revealed by correlation between differential methylation of gene promoters associated with obesity and cardiovascular disease in pregnant women with Firmicutes and Bacteroidetes as the dominant gut microbe groups [82]. Additionally, microbes in the colon are responsible for the conversion of dietary fiber into short-chain fatty acids such as butyrate, which can induce histone hyperacetylation [83] and thereby presenting the potential as a therapeutic agent. Consumption of fat and red meat has been postulated to increase the risk of colorectal cancer through the modulation of N-nitroso compounds and heterocyclic aromatic amines by gut bacteria [84]. In contrast, cruciferous vegetables including cabbage, broccoli, kale and cauliflower have been associated with reduced cancer risk as they contain fiber, lutein, flavonoids, phytosterols folic acid, glucosinolates and vitamin C [85].

Personalized Nutrition

The vast amount of data from bioinformatics and genomics research has strongly revealed the needs for individual and personalized medicine and also nutrition. Individual genetic and epigenetic differences can present dramatic effects on nutritional requirements also in the case of therapeutic interventions. In a case report, a breast cancer patient was not eligible to chemotherapy and radiation treatment due to some severe symptoms [86]. However, specialized testing for metabolic, gastrointestinal and immunological functions revealed nutritional deficiencies in the patient, which after being corrected allowed the necessary chemotherapy and radiation. Nutrigenomics has also substantially influenced tailoring the food intake based on individual genotypes [87]. For example, Korean red ginseng has been applied for the prevention of *H. pylori*-associated gastric cancer [88]. Although nutrigenomics will provide means of genetic basis for nutritional interventions in disease prevention and design of personalized diets accurate evaluation of individual nutritional phenotypes is more complicated [89].

Cancer patients can also profit from dietary modifications. To address the issues of starvation and under-nutrition the areas of 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 have been identified [90]. Moreover, due to suboptimal intake and metabolic disturbances cancer patients often show low concentrations of n-3 fatty acids and can be compensated by n-3 supplementation, which has resulted in improved efficacy and reduced toxicity of chemotherapy [91]. Despite the knowledge of the importance of adequate nutrition in cancer patients, limited attention has been paid within pediatric oncology [92], an issue which should be addressed by a closer interaction between pediatric oncologists and nutrition specialists. Furthermore, zinc deficiency has been discovered to result in oxidative stress and chronic inflammation in many cancers, and for instance in head and neck cancer patients 65% showed zing deficiency [93], which can be addressed relatively easily.

Conclusions and Future Prospects

Epigenetic mechanisms including abnormal DNA methylation, histone modifications and RNAi all contribute significantly to disease development. These findings and the reversible nature of epigenetic modifications have made the epigenome attractive for potential development of novel drugs. Several DNMT and HDAC inhibitors have already been approved as medicines. The recent discovery of the association of a number of miRNAs with various diseases, not the least with cancers, has provided a multitude of new mechanisms and targets for drug discovery.

Furthermore, the strong association between diet and cancer has cast a new light on both prevention and therapy of malignant diseases. Nutritional research and recently the nutrigenomics approach have provided important information on how dietary interventions can affect our well-being and even significantly reduce disease risks. A deeper understanding of genomics has further accelerated development of both personalized nutrition and medicines. The fascinating association of epigenetics with diet and cancer further forms the basis for promises of better opportunities to treat cancer

and most importantly to take preventive actions, which is of outmost necessity from both social and economic aspects.

References

1. Tan EC, Li H. Characterization of frequencies and distribution of single nucleotide insertions/deletions in the human genome. Gene. 2006; 376: 268-280.
2. Smith ED, Tsuchiya M, Fox LA, Dang N, Hu D, Kerr EO, et al. Quantitative evidence for conserved longevity pathways between divergent eukaryotic species. Genome Res. 2008; 18: 564-570.
3. Payton A, Gibbons L, Davidson Y, Ollier W, Rabbitt P, Worthington J, et al. Influence of serotonin transporter gene polymorphisms on cognitive decline and cognitive abilities in a nondemented elderly population. Mol Psychiatry. 2005; 10: 1133-1139.
4. Need AC, Attix DK, McEvoy JM, Cirulli ET, Linney KL, Hunt P, et al. A genome-wide study of common SNPs and CNVs in cognitive performance in the CANTAB. Hum Mol Genet. 2009; 18: 4650-4661.
5. Su LJ, Mahabir S, Ellison GL, McGuinn LA, McGuinn LA, Reid BC. Epigenetic contributions to the relationship between cancer and dietary intake of nutrients, bioactive food components and environmental toxicants. Front Genet. 2012; 2: 91.
6. Fang M, Chen D, Yang CS. Dietary polyphenols may affect DNA methylation. J Nutr. 2007; 137: 223S-228S.
7. Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. Nat Rev Cancer. 2006; 6: 259-269.
8. Horsburgh S, Robson-Ansley P, Adams R, Smith C. Exercise and inflammation-related epigenetic modifications: focus on DNA methylation. Exerc Immunol Rev. 2015; 21: 26-41.
9. White RH, Keberlein M, Jackson V. A mutational mimic analysis of histone H3 post-translational modifications: specific sites influence the conformational state of H3/H4, causing either positive or negative supercoiling of DNA. Biochemistry. 2012; 51: 8173-8188.
10. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Curr Opin Pediatr. 2009; 21: 243-251.
11. Bollati V, Baccarelli A. Environmental epigenetics. Heredity (Edinb). 2010; 105: 105-112.
12. Lundstrom K. Micro-RNA in disease and gene therapy. Curr Drug Discov Technol. 2011; 8: 76-86.
13. Mathers JC, Strathdee G, Relton CL. Induction of epigenetic alterations by dietary and other environmental factors. Adv Genet. 2010; 71: 3-39.
14. www.mirbase.org/cgi-bin/mirna-summary.pl?org=hsa. 2016.
15. Shah PP, Hutchinson LE, Kakar SS. Emerging role of microRNAs in diagnosis and treatment of various diseases including ovarian cancer. J Ovarian Res. 2009; 2: 11.
16. Ong TP, Moreno FS, Ross SA. Targeting the epigenome with bioactive food components for cancer prevention. J Nutrigenet Nutrigenomics. 2011; 4: 275-292.
17. Ross SA, Davis CD. MicroRNA, nutrition, and cancer prevention. Adv Nutr. 2011; 2: 472-485.
18. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 1981; 66: 1191-1308.
19. Boehm TM, Drahovsky D. Alteration of enzymatic methylation of DNA cytosines by chemical carcinogens; a mechanism involved in the initiation of carcinogenesis. J. Natl. Cancer Inst. 1983; 71: 429-433.
20. Costello JF, Plass C. Methylation matters. J Med Genet. 2001; 38: 285-303.
21. Jain N, Rossi A, Garcia-Manero G. Epigenetic therapy of leukemia: An update. Int J Biochem Cell Biol. 2009; 41: 72-80.
22. Banno K, Yanokura M, Iida M, Masuda K, Aoki D. Carcinogenic mechanisms of endometrial cancer: involvement of genetics and epigenetics. J Obstet Gynaecol Res. 2014; 40: 1957-1967.
23. Wang F, Yang Y, Fu Z, Xu N, Chen F, Yin H, et al. Differential DNA methylation status between breast carcinomatous and normal tissues. Biomed Pharmacother. 2014; 68: 699-707.
24. Reyngold M, Turcan S, Giri D, Kannan K, Walsh LA, Viale A, et al. Remodeling of the methylation landscape in breast cancer metastasis. PLoS One. 2014; 9: e103896.
25. Brocks D, Assenov Y, Minner S, Bogatyrova O, Simon R, Koop C, et al. Intratumor DNA methylation heterogeneity reflects clonal evolution in aggressive prostate cancer. Cell Rep. 2014; 8: 798-806.
26. Benard A, Zeestraten EC, Goossens-Beumer IJ, Putter H, van de Velde CJ, Hoon DS, et al. DNA methylation of apoptosis genes in rectal cancer predicts patient survival and tumor recurrence. Apoptosis. 2014; 19: 1581-1593.
27. Shimazu T, Asada K, Charvat H, Kusano C, Otake Y, Katogawa Y, et al. Association of gastric cancer risk factors with DNA methylation levels in gastric mucosa of healthy Japanese: a cross-sectional study. Carcinogenesis. 2015; 36: 1291-1298.
28. White AJ, Sandler DP, Bolick SC, Xu Z, Taylor JA, DeRoo LA. Recreational and household physical activity at different time points and DNA global methylation. Eur J Cancer. 2013; 49: 2199-2206.
29. Luttropp K, Nordfors L, Ekström TJ, Lind L. Physical activity is associated with decreased global DNA methylation in Swedish older individuals. Scand J Clin Lab Invest. 2013; 73: 184-185.
30. Zhang FF, Santella RM, Wolff M, Kappil MA, Markowitz SB, Morabia A. White blood cell global methylation and IL-6 promoter methylation in association with diet and lifestyle risk factors in a cancer-free population. Epigenetics. 2012; 7: 606-614.
31. Kaimori JY, Maehara K, Hayashi-Takanaka Y, Harada A. Histone H4 lysine 20 acetylation is associated with gene repression in human cells. Sci Rep. 2016; 6: 24318.
32. Gnyszka A, Jastrzebski Z, Flis S. DNA methyltransferase inhibitors and their emerging role in epigenetic therapy of cancer. Anticancer Res. 2013; 33: 2989-2996.
33. Ahrens TD, Timme S, Hoeppner J, Ostendorp J, Hembach S, Follo M, et al. Selective inhibition of esophageal cancer cells by combination of HDAC inhibitors and Azacytidine. Epigenetics. 2015; 10: 431-445.
34. Dueñas-Gonzalez A, Coronel J, Cetina L, González-Fierro A, Chavez-Blanco A, Taja-Chayeb L. Hydralazine-valproate: a repositioned drug combination for the epigenetic therapy of cancer. Expert Opin Drug Metab Toxicol. 2014; 10: 1433-1444.
35. Wang LT, Liou JP, Li YH, Liu YM, Pan SL, Teng CM. A novel class I HDAC inhibitor, MPT0G030, induces cell apoptosis and differentiation in human colorectal cancer cells via HDAC1/PKCō and E-cadherin. Oncotarget. 2014; 5: 5651-5662.
36. Apuri S, Sokol L. An overview of investigational Histone deacetylase inhibitors (HDACis) for the treatment of non-Hodgkin's lymphoma. Expert Opin Investig Drugs. 2016.
37. Yoon S, Eom GH. HDAC and HDAC Inhibitor: From Cancer to Cardiovascular Diseases. Chonnam Med J. 2016; 52: 1-11.
38. Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R. FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. Oncologist. 2007; 12: 1247-1252.
39. Valeri N, Braconi C, Gasparini P, Murgia C, Lampis A, Paulus-Hock V, et al. MicroRNA-135b promotes cancer progression by acting as a downstream effector of oncogenic pathways in colon cancer. Cancer Cell. 2014; 25: 469-483.
40. Banno K, Iida M, Yanokura M, Kisu I, Iwata T, Tominaga E, et al. MicroRNA in cervical cancer: OncomiRs and tumor suppressor miRs in diagnosis and treatment. Scientific World Journal. 2014; 2014: 178075.
41. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al. Frequent

deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA. 2002; 99: 15524-15529.

42. He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, et al. A microRNA polycistron as a potential human oncogene. Nature. 2005; 435: 828-833.

43. Iorio MV, Casalini P, Piovan C, Braccioli L, Tagliabue E. Breast cancer and microRNAs: therapeutic impact. Breast. 2011; 20 Suppl 3: S63-70.

44. Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, et al. MicroRNA signatures in human ovarian cancer. Cancer Res. 2007; 67: 8699-8707.

45. Michael MZ, O' Connor SM, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res. 2003; 1: 882-891.

46. Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. Cancer Res. 2005; 65: 6029-6033.

47. Hayashita Y, Osada H, Tatematsu Y, Yamada H, Yanagisawa K, Tomida S, et al. A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation. Cancer Res. 2005; 65: 9628-9632.

48. Chang TC, Wentzel EA, Kent OA, Ramachandran K, Mullendore M, Lee KH, et al. Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. Mol Cell. 2007; 26: 745-752.

49. Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci U S A. 2005; 102: 13944-13949.

50. Ng JM, Yu J. Promoter hypermethylation of tumour suppressor genes as potential biomarkers in colorectal cancer. Int J Mol Sci. 2015; 16: 2472-2496.

51. Koppers-Lalic D, Hackenberg M, Menezes R, Misovic B, Wachalska M, Geldof A. Non-invasive prostate cancer detection by measuring miRNA variants (isomiRs) in urine extracellular vesicles. Oncotarget. 2016.

52. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 1981; 66: 1191-1308.

53. World Cancer Research Fund, American Institute of Cancer Research. Diet, Nutrition and Prevention of Human Cancer: A Global Perspective, World Cancer Research Fund, Washington, American Institute of Cancer Research. 2007.

54. Ouédraogo M, Charles C, Ouédraogo M, Guissou IP, Stévigny C, Duez P. An overview of cancer chemopreventive potential and safety of proanthocyanidins. Nutr Cancer. 2011; 63: 1163-1173.

55. Ferguson LR. Nutrigenomics approaches to functional foods. J Am Diet Assoc. 2009; 109: 452-458.

56. Lampe JW. Interindividual differences in response to plant-based diets: implications for cancer risk. Am J Clin Nutr. 2009; 89: 1553S-1557S.

57. Milner JA. Nutrition and cancer: essential elements for a roadmap. Cancer Lett. 2008; 269: 189-198.

58. Krakowsky RH, Tollefsbol TO. Impact of Nutrition on Non-Coding RNA Epigenetics in Breast and Gynecological Cancer. Front Nutr. 2015; 2: 16.

59. Hargraves KG, He L, Firestone GL. Phytochemical regulation of the tumor suppressive microRNA, miR-34a, by p53-dependent and independent responses in human breast cancer cells. Mol Carcinog. 2016; 55: 486-498.

60. Rossi EL, de Angel RE, Bowers LW, Khatib SA, Smith LA, Van Buren E, et al. Obesity-Associated Alterations in Inflammation, Epigenetics, and Mammary Tumor Growth Persist in Formerly Obese Mice. Cancer Prev Res (Phila). 2016.

61. Jiang Y, Pan Y, Rhea PR, Tan L, Gagea M, Cohen L, et al. A Sucrose-Enriched Diet Promotes Tumorigenesis in Mammary Gland in Part through the 12-Lipoxygenase Pathway. Cancer Res. 2016; 76: 24-29.

62. Dong JY, He K, Wang P, Qin LQ. Dietary fiber intake and risk of breast cancer: a meta-analysis of prospective cohort studies. Am J Clin Nutr. 2011; 94: 900-905.

63. Dong JY, Zhang L, He K, Qin LQ. Dairy consumption and risk of breast cancer: a meta-analysis of prospective cohort studies. Breast Cancer Res Treat. 2011; 127: 23-31.

64. Dong JY, Qin LQ. Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. Breast Cancer Res Treat. 2011; 125: 315-323.

65. Huzarski T, Byrski T, Gronwald J, Kowalska E, Zajaczek S, Górski B, et al. A Lowering of Breast and Ovarian Cancer Risk in Women with a BRCA1 Mutation by Selenium Supplementation of Diet. Hered Cancer Clin Pract. 2006; 4: 58.

66. Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalder B, Bartsch H. The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. Eur J Cancer. 2000; 36: 1235-1247.

67. Di Francesco A, Falconi A, Di Germanio C, Micioni Di Bonaventura MV, Costa A, Caramuta S, et al. Extravirgin olive oil up-regulates CB_1, tumor suppressor gene in human colon cancer cells and in rat colon via epigenetic mechanisms. J Nutr Biochem. 2015; 26: 250-258.

68. Chen L, Chen H, Li Y, Li L, Qiu Y, Ren J. Endocannabinoid and ceramide levels are altered in patients with colorectal cancer. Oncol Rep. 2015; 34: 447-454.

69. Labbé DP, Zadra G, Ebot EM, Mucci LA. Role of diet in prostate cancer: the epigenetic link. Oncogene. 2015; 34: 4683-4691.

70. Supic G, Jagodic M, Magic Z. Epigenetics: a new link between nutrition and cancer. Nutr Cancer. 2013; 65: 781-792.

71. Kikuno N, Shiina H, Urakami S, Kawamoto K, Hirata H, Tanaka Y, et al. Genistein mediated histone acetylation and demethylation activates tumor suppressor genes in prostate cancer cells. Int J Cancer. 2008; 123: 552-560.

72. Majid S, Kikuno N, Nelles, J, Noonan E, Tanaka Y, Kawamoto K, et al. Genestein induces the p21WAF1/CIP1 and p16INK4a tumor suppressor genes in prostate cancer cells by epigenetic mechanisms involving active chromatin modification. Cancer Res. 2008; 68: 2736-2744.

73. Pandey M, Kaur P, Shukla S, Abbas A, Fu P, Gupta S. Plant flavone apigenin inhibits HDAC and remodels chromatin to induce growth arrest and apoptosis in human prostate cancer cells: *in vitro* and *in vivo* study. Mol. Carcinog. 2012; 51: 952-962.

74. Kumar A, Dhar S, Rimando AM, Lage JM, Lewin JR, Zhang X, et al. Epigenetic potential of resveratrol and analogs in preclinical models of prostate cancer. Ann N Y Acad Sci. 2015; 1348: 1-9.

75. Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci USA. 2008; 105: 8369-8374.

76. Jeurnink SM, Büchner FL, Bueno-de-Mesquita HB, Siersema PD, Boshuizen HC, Numans ME, et al. Variety in vegetable and fruit consumption and the risk of gastric and esophageal cancer in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2012; 131: E963-973.

77. Cooper R. Green tea and theanine: health benefits. Int J Food Sci Nutr. 2012; 63 Suppl 1: 90-97.

78. Annema N, Heyworth JS, McNaughton SA, Iacopetta B, Fritschi L. Fruit and vegetable consumption and the risk of proximal colon, distal colon, and rectal cancers in a case-control study in Western Australia. J Am Diet Assoc. 2011; 111: 1479-1490.

79. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Vegetables and fruits consumption and risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. Int J Cancer. 2011; 129: 2681-2693.

80. Paul B, Barnes S, Demark-Wahnefried W, Morrow C, Salvador C, Skibola C, et al. Influences of diet and the gut microbiome on epigenetic modulation in cancer and other diseases. Clin Epigenetics. 2015; 7: 112.

81. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med. 2009; 1: 6ra14.

82. Kumar H, Lund R, Laiho A, Lundelin K, Ley RE, Isolauri E, et al. Gut microbiota as an epigenetic regulator: pilot study based on whole-genome methylation analysis. MBio. 2014; 5.

83. Candido EP, Reeves R, Davie JR. Sodium butyrate inhibits histone deacetylation in cultured cells. Cell. 1978; 14: 105-113.

84. Hughes R, Cross AJ, Pollock JR, Bingham S. Dose-dependent effect of dietary meat on endogenous colonic N-nitrosation. Carcinogenesis. 2001; 22: 199-202.

85. Herr I, Büchler MW. Dietary constituents of broccoli and other cruciferous vegetables: implications for prevention and therapy of cancer. Cancer Treat Rev. 2010; 36: 377-383.

86. Plotnikoff GA. Interventional nutrition in cancer survivorship. A case study. Minn Med. 2010; 93: 53-58.

87. Farooqi AA, Rana A, Riaz AM, Khan A, Ali M, Javed S, et al. NutriTRAILomics in prostate cancer: time to have two strings to one's bow. Mol Biol Rep. 2012; 39: 4909-4914.

88. Won I, Kim YJ, Kim SJ, Kim EH, Hahm KB. Nutrigenomic approach to tackle the unpleasant journey to Helicobacter pylori-associated gastric carcinogenesis. J Dig Dis. 2011; 12: 157-164.

89. German JB, Zivkovic AM, Dallas DC, Smilowitz JT. Nutrigenomics and personalized diets: What will they mean for food? Annu Rev Food Sci Technol. 2011; 2: 97-123.

90. Bozzetti F. Nutritional support in oncologic patients: where we are and where we are going. Clin Nutr. 2011; 30: 714-717.

91. Murphy RA, Mourtzakis M, Mazurak VC. n-3 polyunsaturated fatty acids: the potential role for supplementation in cancer. Curr Opin Clin Nutr Metab Care. 2012; 15: 246-251.

92. Bauer J, Jürgens H, Frühwald MC. Important aspects of nutrition in children with cancer. Adv Nutr. 2011; 2: 67-77.

93. Prasad AS, Beck FW, Snell DC, Kucuk O. Zinc in cancer prevention. Nutr Cancer. 2009; 61: 879-887.

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