ReviewArticle

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The Effect of Dietary Constituents on Regulation of Epigenetic Changes in Cancer

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ABSTRACT

BACKGROUND AND OBJECTIVE: The term "epigenetic" refers to all non-heritable and reversible changes in the expression of a gene that does not cause a change in the DNA sequence. The most important epigenetic mechanisms associated with gene expression include DNA methylation, histone modifications, and suppression of gene expression with RNA. Considering the reversibility of epigenetic changes, it seems that this feature can be influenced by dietary constituents and thus, we can prevent the spread of certain cancers by controlling the diet. The purpose of this study is to investigate the effects of food on the prevention of common cancers and the mechanisms involved in cellular activities based on recent studies and the compilation of their results.

METHODS: In this review article, we searched Pubmed and Elsevier databases using certain keywords such as "epigenetics", "cancer" and "nutrition" and articles related to the effects of epigenetics on cancer and dietary constituents were evaluated.

FINDINGS: Of 439 studies found in the search engines between 1997 and 2016, 64 articles were selected and their results indicated that many of the active components in the diet will inhibit the incidence of cancer through DNA methylation mechanisms, histone modifications, and miRNA.

CONCLUSION: The anticancer effect of the active compounds in the diet on specific epigenetic changes can be used as a special and unidentified mechanism for preventing cancer.

KEY WORDS: *Epigenetic, Cancer, Nutrition.*

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Introduction

Epigenetic changes are inherited changes in gene expression that do not change the DNA sequence (1). There is a lot of evidence indicating that there is a relationship between epigenetic disorders and various diseases, including cancer, multiple sclerosis (2), diabetes (3), and obesity. Recent studies show the effects of dietary compounds on the cancer process. The isothiocyanate in the family of cabbage (cauliflower, broccoli), diallyl sulfide (organosulfur compound in garlic), isoflavone, phytosterol, theophylline, folate, selenium, vitamin E, flavonoids and dietary fiber may reduce the risk of cancer (4, 5). The main mechanisms of epigenetic control in mammals include DNA methylation, histone modifications, and RNA interferences (6, 7).

The key to epigenetic changes in mammals is the addition of a 5-methylcytosine group in two nucleotide sequences of CPG (1, 8). The CPG sequences are CG-rich regions known as CPG islands and are associated with transcriptional initiation regions (6, 8). Hypermethylation of these regions can lead to silencing of transcription of tumor suppressor genes and their inactivation in various cancers (1).

The addition of covalent methyl group is catalyzed by DNA methyltransferase family (DNMTs), which utilizes S-Adenosyl methionine (SAM) as a methyl group provider (8). DNMT1 is initially involved in the storage of DNA methylation after replication, and DNMT3A and DNMT3B interact with the transcriptional machine and mediate methylation. Several studies have shown that DNMTs can be expressed in a number of cancers (8). The purpose of this study is to investigate the effects of food on the prevention of common cancers and the mechanisms involved in cellular activities based on recent studies and the compilation of their results.

Methods

In this review article, the effect of food on the cancer formation process using the key words “Epigenetic”, “Cancer” and “Nutrition”, the scientific articles indexed in Pubmed and Elsevier databases between 1997 and 2016 were reviewed and the articles were carefully evaluated.

Results

439 articles were extracted in relation to the keywords, among which 64 articles were selected and reviewed. Articles that examined the effects of other factors such as age or the presence of environmental factors such as UV were excluded. According to these studies, active food compound cause epigenetic changes with mechanisms such as DNA methylation in progesterone CPGs, histone modifications, and miRNA expression.

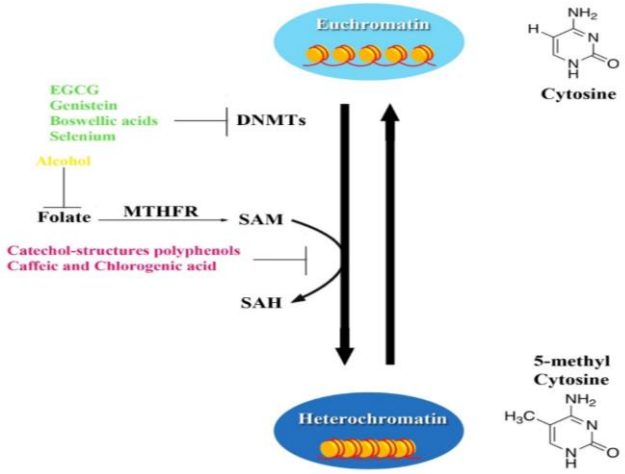

Figure 1. DNA methylation in the cytosine of the CPG island promoters leads to silencing of transcription of tumor suppressor genes and their malignant changes

Dietary compounds, DNA methylation and hereditary epigenetic changes: A number of epidemiological studies associate adverse environmental and nutritional conditions in the early stages of growth and embryonic development, and then at puberty, with the risk of developing certain diseases in adulthood. Although the underlying mechanism of this relationship is still unknown, evidence suggests interference with epigenetic disorders (8–11).

Dietary compounds and DNA methylation in cancer: Compounds such as folate, tea polyphenols, soy isoflavones and catechol polyphenols have anti-cancer properties with DNA methylation mechanisms (12, 13) (Fig 1). Folate is involved in the metabolism of single-carbon units, DNA synthesis and DNA methylation (14). Folate deficiency causes cancer though DNA damage (inappropriate uracil pairing) (15, 16), ectopic methylation, such as promoter methylation (17, 18), and DNMT1 inhibition (19). Enriching a diet with folic acid or natural folate reduces the risk of colorectal cancer (20, 21). Additionally, its high doses (20 mg folate/kg) significantly decrease the polyps of the intestine in Apc $^{Min/+}$ mice after 3 months. However, after 6 months, supplementation with folate has an opposite effect on the number of polyps in the intestine (22). In a study, folic acid deficiency in mothers was

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associated with DNA ectopic methylation, which leads to neural tube defects. Low levels of folate in the serum of mothers are associated with DNA hypomethylation in the brain and DNA hypermethylation in the skin and fetal heart that is associated with neural tube defects (23).

EGCG is the main polyphenol in green tea with antioxidant properties that can inhibit tumor metastasis and angiogenesis (24). Epidemiological studies have shown that using green tea reduces the risk of hepatocellular carcinoma (25). EGCG directly or indirectly inhibits DNMT (26). Treatment of human cancer cells, esophageal cancer cells KYSE510, HT-29 colon cancer, and PC3-induced prostate cancer with EGCG result in the return of hypermethylation of p16, RARβ, and MGMT genes (27).

Treatment of Caco-2 cells with EGCG inhibits cellular growth and inhibits the promoter's methylation of anti-tumor genes p16 and P15 (28). Treatment of breast cancer cell line MCF-7 and promyelocytic leukemia cells with EGCC have the potential to reduce cell proliferation and induction of apoptosis (29). In fact, EGCG is effective in both antioxidant and epigenetic changes to various cancer cells. However, the potential harmful effects of high consumption of green tea (DNA hypomethylation and oncogene activation and genomic instability) should be taken into account.

Genistein (soy isoflavone) has the effects of cancer prevention through epigenetic mechanisms (30). Genistein causes the reversal of DNA methylation and re-activation of RARß and MGMT genes in KYSE510 cells (31), and at high doses, it inhibits the DNA of methyl transferases in LNcap and PC3 cell lines in prostate cancer (32).

These findings indicate that genistein activates tumor suppressor genes that have been silenced. Resveratrol is a natural phytoalloxin compound that the ability to inhibit proliferation of cells, which increases the methylation of P16 and reduces the methylation of P15 in Caco2 cells (28).

Curcumin (Curcuma longa rhizome flavonoid) also has anticancer activity. Curcumin and genistein cause the reversal of the RARß2 gene hypermethylation in the cervical cancer cell line SiHa and HeLa, as well as progressive demethylation (33). Quercetin is a flavonoid with antioxidant and anti-proliferative activity, which is a natural inhibitor of catechol-O-methyl transferase (COMT). Quercetin induces cell cycle stoppage and apoptosis of the hamster's oral tumor, and the effect is related to the control of DNMT1 (33). Quercetin also increases the bioavailability of green tea polyphenols in the investigation of the A549 and O-786 cell lines, as well as in mice with immunodeficiency (34).

In addition, quercetin boosts anti-proliferative activity of EGCG by increasing intracellular EGCG concentration and reducing methylation in prostate cancer cells (35). Selenium is an essential ingredient that has potential for preventing cancer due to antioxidant and pro-apoptotic effects (31, 36). Treatment of Caco2 cells with selenite induces total hypomethylation and promoter methylation of the P53 gene (36).

Selenium plays an anticancer role in human colon cancer through DNMT inhibition (37). However, selenium and vitamin E inhibitors did not provide evidence to prove that selenium prevents prostate, lung, or colorectal cancers (38).

Changes after histone translation: Histones have an active function in regulating chromatin structure and gene expression. Histone tails may change by acetylation, Methylation, Phosphorylation, Poly ADP-Ribosylation, sumoylation, or ubiquitination (6, 39). DNA methylation and histone modification are not independent events.

The methylation of cytosine in CPG islands is associated with the attachment between binding proteins and methyl cytosine, followed by catalytic enzymes of histone modifications (1, 6). Acetylation in histone lysine amino group neutralizes the positive lysine load by histone acetyltransferases (HATs) and releases the histone tail of the negatively charged DNA. These changes lead to access to transcription factors for the expression of genes in that area (6). Histone deacetylases leads to chromatin congestion and transcription inhibition by histone deacetylases (HDACs). In the deacetylated state, the amine lysine group has a positive charge and allows the tail of the histone to interact strongly with the DNA strand that has a negative charge (40, 41).

Methylation of the roots of lysine and arginine in H3 and H4 histones can have suppressive and transcriptional effects depending on the type of amino acid and its position. Histone methylation without changing the histone load changes its chemical properties and thus affects the tendency for regulatory proteins. Histone methylation is catalyzed by histone methyltransferases, while the omission of methyl groups is catalyzed by histone demethylase (42)

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(Fig2). H1 phosphorylation weakens its binding to DNA and gives free access to transcription factors and gene expression. Histonomic phosphorylation is observed in a number of cancers, such as breast, prostate and colorectal cancer (39).

Dietary compounds and histone modifications in cancer: Folate can affect the methylation of histones in cancer. A diet that is low in methyl donors leads to changes in H4-K20 methylation and H3-K9 acetylation, which is usually observed in liver cancer (43). EGCG induces changes in human A431 melanoma cells. EGCG reduces the deacetylation activity of histone and increases lysine acetylation in histones 4 and 3 and reduces lysine 9 histone 3 methylation (44).

In the MCF-7 cells, genistein reduces the histone 3 acetylation and induces growth response to mitogens and histone deacetylase (HDAC) inhibitors (45). In the MCF-7 breast cancer cell line, resveratrol inhibits the dioxin-induced histone modifications in the BRCA-1 gene and suppresses the expression of BRCA1 protein, decreasing the DNA fragmentation associated with dioxin (46).

Treatment of brain cancer cells with curcumin causes hypomethylation of H3 and H4 histones (47). Conversely, in prostate cancer cells, curcumin induces acetylation of H3 and H4 and also causes apoptosis through Bcl2 and P53 families (48).

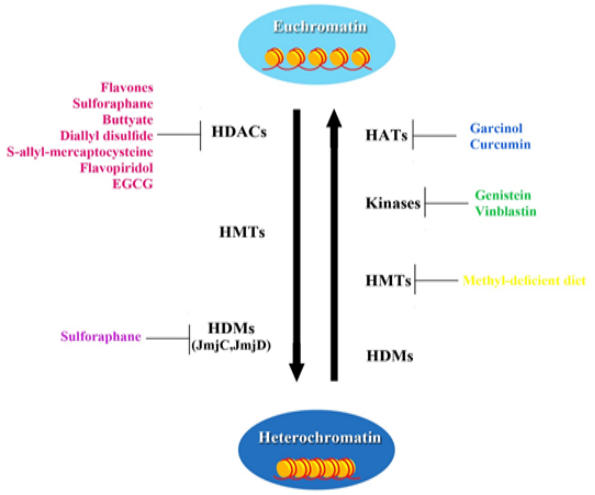

Figure 2. Histone modifications determine the interaction of histones with DNA and the interaction of non-histone proteins with chromatin

RNA-related silence by microRNAs in cancer: Micro-RNAs or miRNAs play a role in the post-transcriptional configuration by binding to the non-translatable region of the target 3' (3′UTR) mRNA (49, 50). MiRNA acts in two ways: full pairing with complementary cells that results in the destruction of the target mRNA, and partial pairing that results in inhibiting the translation of the target mRNA (49, 50) (Fig 3). In addition, they also play a role in transcriptional regulation, which can bind to complementary sequences in the genome and induce gene silencing through the administration of suppressor proteins and induction of symptoms of chromatin suppression (51, 52). Changes in the expression of miRNAs are a common occurrence in cancer. Some of them act as suppressor tumors of hypothetical genes, and some as oncogenes (49, 50).

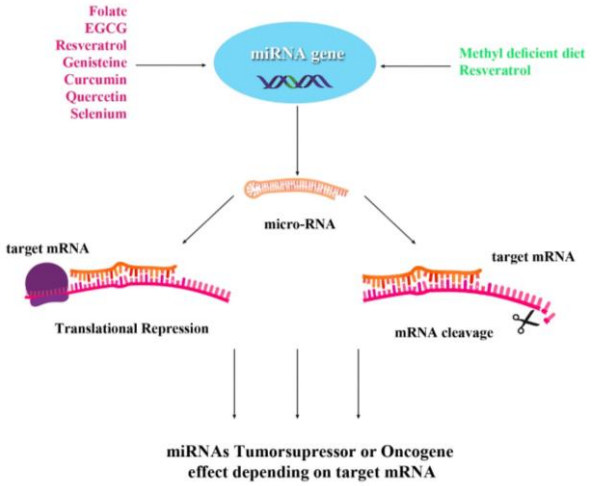

Figure 3. MiRNAs are small and noncoding RNAs that contribute to post-transcription regulation through binding to the target mRNA

Dietary components and miRNA changes in cancer: Nutrition, lifestyle and genetic factors also affect the risk of cancer through miRNAs (Fig. 3). Fat-rich diets in mothers before fertilization, during pregnancy and breastfeeding induces long-term changes in IGF2 expression (11). Folate deficiency leads to a general increase in the expression of miRNA in lymphocyte (53). The hepatocarcinogenesis of methyl deficiency in mice results in reduced expression of miRNA gene (54, 55), including miRNA-34a and miRNA-127, which are involved in apoptosis and cell proliferation, respectively (56).

In addition, folic acid supplement inhibits the expression of miRNA-10a induced by alcohol use (57). EGCG modifies the expression of a number of miRNAs in human hepatocyte carcinoma, including miRNA-16, which targets the anti-apoptotic protein Bcl-2 (58). Treatment with uveal melanoma cells with genistein decreases cell proliferation and increases the

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expression of miRNA-27a (59). In BALB / C nu / nu mice, genistein significantly inhibits the growth of the human uveal melanoma xenografts (59). The treatment of the colon cancer cell line SW480 with resveratrol reduces the level of several oncogene miRNAs targeting PTEN and PDCD4 (60). Simultaneously, this treatment increases the amount of miR-663 that targets the TGFβ growth factor transcript (61).

Treatment of BxPC-3 human pancreatic cancer cells with curcumin increases the expression of miRNA22 and decreases expression of miRNA-199a (62). Quercetin induces miR-146a, a negative regulator of pro-inflammatory NF-kB activity in HT-29 colon cancer cells (63). The treatment of LNCaP prostate cancer cells with selenite-induced p53 induces apoptosis and expresses miR-34 that targets the P53 transcript (64).

Discussion

This study shows that active compounds are effective on DNA methylation, histone modifications, and miRNA expression in cancer. However, it is unlikely that the protective effects would be caused by only one dietary component. Therefore, identification of relevant compounds and metabolites is required. Another key issue is the appropriate concentrations of herbal compounds for inducing optimal epigenetic modifications (6).

Epigenetic changes in tissue are important for cellular differentiation. Thus, active food components may cause different epigenetic changes in different tissues and even different types of cells in a tissue. In addition, epigenetic changes induced by food components can be temporary. Therefore, it is important to recognize the specific effects of the cell and tissue of an active dietary compound and related kinetics. The development of relevant animal tissue culture models is necessary to study the effects of diet and the environment on epigenetic changes to clarify their relationship and their interaction potential.

The complex interactions between environmental, genetic and epigenetic factors during cancer development have not been thoroughly defined. However, the definition of bioactive food components is necessary to provide safe dietary advice and to determine the dose required for preventative effects. Therefore, further studies are needed to identify epigenetic changes and cellular features and time patterns. Nevertheless, despite so many unresolved questions, there is a promising future for dietary recommendations on cancer prevention and the provision of natural-based treatment programs for cancer treatment.

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