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Mini-Review

Associations of Dietary Methyl-Group Donors with Epigenetics through One-Carbon Metabolism in Breast Cancer Risk

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Abstract

In Japan, age-specific incidence rates of breast cancer exhibited an increase trend from 2005 to 2015, showing a bimodal distribution pattern with pre- and postmenopausal peaks. This suggests the involvement of modifiable lifestyle factors in the development and progression of breast cancer. Epigenetic changes, such as DNA methylation and histone modifications, could play a crucial role in these processes. Certain nutrients, including folate and methionine, act as methyl-group donors within the one-carbon metabolism pathway, contributing to histone and DNA methylation. In this mini-review, we provide a brief overview of epigenetic modifications, particularly in relation to one-carbon metabolism, and explore the potential impact of dietary methyl-group donor intake on breast cancer risk. Overall, the influence of dietary intake of folate or methionine on breast cancer risk may exhibit a potential U-shaped relationship. However, the exact contribution of methyl-group donors through epigenetics to breast cancer development remains somewhat illusive. The metabolic network involved in one-carbon metabolism suggests that high folate or methionine intake may contribute to breast cancer progression. As breast cancer incidence continues to rise among Asian women, further research on the interactions between nutrition and epigenetics, which may be reversible, is expected to advance breast cancer prevention and treatment.

Keywords: Breast Cancer; Epigenetics, Folate; Methionine, One-Carbon Metabolism

Introduction

Breast cancer is the most prevalent cancer worldwide, accounting for a quarter of all cancer cases in women. In 2020, approximately 2.3 million cases of breast cancer were diagnosed, resulting in approximately 685,000 deaths [1]. Interestingly, cross-sectional age-specific incidence rates of breast cancer among Western women continuously rose until age 80, while among Asian women, they plateaued or decreased after age 50. However, the longitudinal incidence rates have shown a rapid increase in Asian countries [2]. In Japan, age-specific incidence rates of breast cancer exhibited an increase from 2005 to 2015 in a bimodal distribution pattern with pre- and postmenopausal peaks [3]. Estrogen is considered to contribute to the carcinogenesis of breast cancer through estrogen metabolism and estrogen receptor pathways [4]. Besides estrogen-related factors, breast cancer risk is associated with various modifiable lifestyle factors, including diet, physical activity, smoking, and alcohol consumption [5].

The development of cancer usually involves the accumulation of mutations caused by inherited and environmental factors, particularly DNA replication errors in tissue-specific stem cells [6,7]. In addition to oncogenic mutations, epigenetic changes, which refer to dynamic and heritable modifications of the genome without altering the DNA sequence, could play an important role in cancer development [8,9]. DNA methylation and histone modifications among epigenetic changes are considered crucial in the development and progression of breast cancer [10,11]. Certain nutrients, including folate and methionine, act as methyl-group donors within the one-carbon metabolism pathway, contributing to histone and DNA methylation [12,13]. In this mini-review, we provide a brief overview of epigenetic modifications, particularly in relation to one-carbon metabolism, and then explore the potential effect of dietary methyl-group donor intake on breast cancer risk.

Epigenetics in cancer

The activation of oncogenes and the inactivation of tumor suppressor genes are crucial processes for cancer development and progression, often accompanied by epigenetic changes, such as DNA methylation, histone modifications and non-coding RNAs [11,14]. Figure 1 illustrates epigenetic modifications. The genome, carrying the DNA sequence, condenses into chromatin with histone proteins. The nucleosome, the basic unit of chromatin, comprises eight histone proteins (two copies of H2A/H2B dimer cores and H3/H4 tetramers) that wrap around approximately 146 base pairs of the DNA [11,15]. DNA methylation involves the covalent addition of a methyl group to cytosine residues, usually occurring in CpG dinucleotides. Hypermethylation of CpG islands in the promoter regions of tumor-suppressor genes leads to gene repression and is

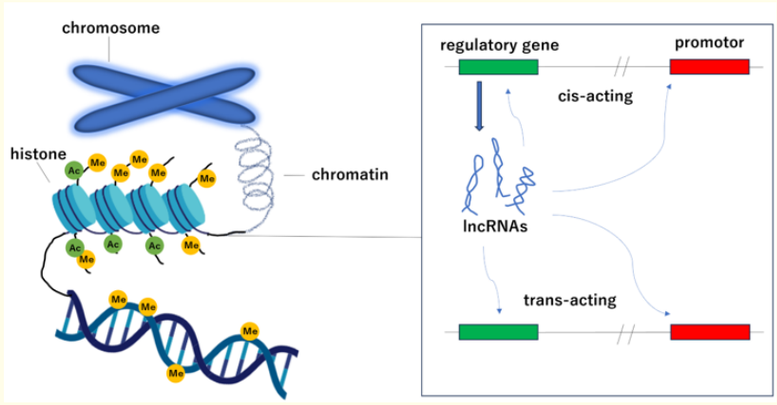

Figure 1: Epigenetic modifications of DNA methylation, histone modifications and non-coding RNAs. The nucleosome, the basic unit of chromatin, is composed of eight histone proteins that wrap around approximately 146 base pairs of DNA. DNA methylation involves the covalent addition of a methyl group to cytosine residues, typically occurring in CpG dinucleotides. Hypermethylation of CpG islands in promoter regions represses gene expression. Histone tails undergo post-translational modifications, such as lysine acetylation or methylation, which regulate DNA transcription. As a putative mechanism of non-coding RNAs, long non-coding RNAs (lncRNAs) transcribed from the regulatory region can regulate gene expression either by cis- or trans-acting on the regulatory gene or the promoter of the target gene. Ac: acetylation, Me: methylation.

observed in many cancers, including breast cancer involving BRCA1 (breast-cancer susceptibility gene 1) [14,16]. On the other hand, DNA hypomethylation can result in gene reactivation and chromosome instability, leading to oncogene overexpression [17,18]. Non-coding RNAs, both short and long, can regulate gene expression in a sequence-dependent or -independent manner [18,19]. In breast cancer studies, long non-coding RNAs have been demonstrated to be involved in various molecular mechanisms, such as chromatin regulation and enhancer-like functions [19].

DNA methylation is associated with histone protein modifications that play a role in the regulation of gene expression. For instance, the interaction between Polycom group proteins and Trithorax group of histone methyltransferases is implicated in this process [8,14,20]. Histone tails undergo post-translational modifications, including lysine acetylation, arginine or lysine methylation (mono-, di- and tri-methylation), and serine phosphorylation, resulting in a "histone code" [21]. Lysine acetylation is associated with active chromatin structure, while lysine methylation (histone 3 lysine 4 (H3K4) or H3K9, H3K27, and H4K20) can be linked to either active or repressive states of chromatin structure (euchromatic or heterochromatic state). Enzymatic actions of histone acetyltransferases or deacetylases, as well as histone methyltransferases or demethylases, catalyze the dynamics of histone protein modifications. Some of these are associated with nucleosomal remodeling complexes [8].

One-carbon metabolism and epigenetics

DNA and histone protein methylation is presumed to play crucial roles in silencing tumor-suppressor genes during cancer development and progression. These methylation reactions are regulated by the universal methyl donor, S-adenosylmethionine, which is produced through one-carbon metabolism consisting of the folate and methionine cycles (Figure 2) [12,13]. S-adenosylmethionine is synthesized from methionine and ATP by methionine adenosyltransferase, and methionine is regenerated from homocysteine by betaine-homocysteine methyltransferase or 5-methyltetrahydrofolate-homocysteine methyltransferase. Multiple forms of folate cofactors act as methyl group carriers by accepting them from serine to form methionine [13]. In addition to its role in methylation metabolism, one-carbon metabolism transfers single carbon units to acceptor substrates, connecting to the maintenance of cellular redox and the cellular biosynthesis of nucleotides, phospholipids, and polyamines [12,22,23].

Several compounds within one-carbon metabolism, such as folate, vitamin B12, vitamin B6, betaine, choline (a precursor of betaine) and methionine, serve as methyl acceptors or donors [12,13]. DNA methylation is the most extensively studied form of epigenetic modification, relying on various enzymes that require dietary micronutrients as cofactors [24]. It is plausible that these nutrients from the diet can affect histone tail methylation, in addition to DNA methylation. Indeed, studies demonstrated that folate and methionine deficiency was associated with reduced histone methylation, particularly H3K4 methylation, in yeast and human cells [25].

Methyl-group donors and breast cancer risk

The intake of folate, choline, betaine and methionine has been suggested to have a role in breast cancer risk through epigenetic mechanisms [12,13]. These nutrients act as methyl-group donors within the one-carbon metabolism pathway, ultimately providing readily usable methyl units in the form of S-adenosylmethionine [13,24,26]. Among these, folate has been extensively studied in relation to breast cancer risk. In East Asia, higher intake of folate

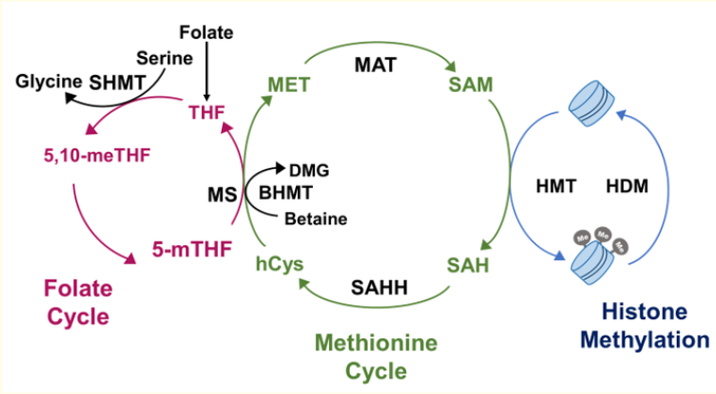

Figure 2: One-carbon metabolism of the methionine and folate cycles. The methionine cycle is crucial for generating the universal methyl donor, S-adenosylmethionine (SAM), by methionine adenosyltransferase (MAT). Histone methyltransferases (HMT) transfers methyl groups from SAM to histone proteins, leading to the production of S-adenosylhomocysteine (SAH). Betaine-homocysteine methyltransferase (BHMT) transfers a methyl group from betaine to homocysteine (hCys) to regenerate methionine (MET). 5-Methyltetrahydrofolate-homocysteine methyltransferase (MS) catalyzes the transfer of a methyl group from 5-methyltetrahydrofolate (5-mTHF) to hCys, resulting in the production of tetrahydrofolate (THF) and the regeneration of MET. SAHH: S-adenosylhomocysteine hydrolase, DMG: dimethylglycine, SHMT: serine hydroxymethyltransferase, 5,10-meTHF: 5,10-methylenetetrahydrofolate, HDM: histone demethylase.

was associated with decreased breast cancer risk among Japanese women (odds ratio, 0.79) [27] and among Chinese premenopausal women (hazard ratio, 0.58) [28], but was associated with a poor prognosis of breast cancer among Korean women with estrogen receptor-negative breast cancer [29]. There is conflicting evidence on the association [30,31], with some studies suggesting a J-shaped [32] or U-shaped relationship [26,33,34]. Such relationships indicates that there may be an optimal folate intake for breast cancer prevention, and excessive intake may lead to the progression of pre-existing tumor cells [35]. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study [26], decreased breast cancer risk was observed for dietary folate intakes up to 350 μg/day, compared to the reference intake of 205 μg/day. Alcohol consumption can also influence DNA methylation patterns, through its impact on the S-adenosylmethionine availability, reducing folate levels, and inhibition of key enzymes in one-carbon metabolism [36].

As for methionine, a meta-analysis of published observational studies indicated an inverse association between dietary methionine intake and breast cancer risk among postmenopausal women (relative risk, 0.94), but not among premenopausal women [37]. However, a prospective cohort study showed that decreased methionine intake after breast cancer diagnosis was associated with lower risk of all-cause and breast cancer mortality [38]. Methionine restriction has been known to extend lifespan and inhibit cancer cell growth, across different species, but the underlying mechanisms are not fully understood [23,39,40]. Although methionine is essential for normal growth and development, methionine restriction may be involved in extending lifespan induced by caloric restriction [41,42]. Therefore, the association of dietary methionine intake with breast cancer risk may also exhibit a U-shaped relationship, similar to folate. Choline and betaine, as methyl-group donors in the reaction converting homocysteine to methionine, was inversely associated with the risk of breast cancer among Chinese women [43]. However, in the EPIC study [26], individual dietary intakes of methionine, choline, and betaine showed no linear association with breast cancer risk. Interestingly, a study on esophageal cancer in Japan found that higher dietary methionine intake was associated with an increased risk (hazard ratio, 3.45) of esophageal cancer among non-drinkers (most of the non-drinkers were presumably women in Japan [44]), while there was no such association with folate intake [45]. Among all participants in this study, the mean methionine intakes were 1.2 g/day for the lowest quintile (non-drinkers, 47%) and 2.2 g/day for the highest quintile (non-drinkers, 54%).

Table 1 summarizes the epidemiological studies on the association between dietary folate or methionine intake with breast cancer risk or progression, with two additional case-control studies [46,47]. One study demonstrated that increased breast cancer risk was observed among Brazilian premenopausal women with high folate intake (odds ratio, 2.17) [46]. Another study demonstrated an inverse association between natural food folate intake and estrogen-positive breast cancer risk among African American women (odds ratio, 0.58), and a positive association between synthetic folate intake from fortified foods and breast cancer risk among European American women (odds ratio, 1.53) [47]. In this study, the amount of synthetic folate intake was approximately 30% of total folate intake. Overall, the influence of dietary folate or methionine intake on breast cancer risk remains inconclusive, and the contribution of methyl-group donors through epigenetics to breast cancer development remains somewhat illusive. Considering the metabolic network involved in one-carbon metabolism, it is plausible that high folate or methionine intake can contribute

Authors	Country	Study	Results	Ref.
Puyvelde HV., *et al*.	Europe	Prospective cohort	Potential U-shaped relationship between folate intake and breast cancer risk. Decreased risk for intakes up to 350 µg/day (reference intake of 205 µg/day).	26
Islam T., *et al*.	Japan	Case-control	High folate intake was associated with decreased breast cancer risk among Japanese women (odds ratio, 0.79).	27
Shrubsole MJ., *et al*.	China	Prospective cohort	High folate intake was associated with decreased breast cancer risk among Chinese premenopausal women (hazard ratio, 0.58).	28
Lee Y., *et al*.	Korea	Prospective case	High folate intake was associated with breast cancer progression among Korean women with estrogen receptor-negative breast cancer.	29
Ma E., *et al*.	Brazil	Case-control	High folate intake was associated with increased breast cancer risk among Brazilian premenopausal women (odds ratio, 2.17).	46
Gong Z., *et al*.	USA	Case-control	High folate intake from natural foods was associated with decreased breast cancer risk among African American women (odds ratio, 0.58). High synthetic folate intake from fortified foods was associated with increased breast cancer risk among European American women (odds ratio, 1.53).	47
Wu W., *et al*.	USA, China, elsewhere	Meta-analysis	High methionine intake was associated with decreased breast cancer risk among postmenopausal women (relative risk, 0.94).	37
Sun Y., *et al*.	USA	Prospective case	Decreased methionine intake after breast cancer diagnosis was associated with low risk of all-cause and breast cancer mortality among American postmenopausal women.	38

Table 1. Epidemiological studies on the association of dietary folate or methionine intake with breast cancer risk or progression.

to breast cancer progression. Further experimental and epidemiological studies are needed to better understand the potential U-shaped relationship between dietary folate or methionine intake and breast cancer risk.

Conclusion

Epigenetic changes involving DNA methylation and histone modifications appear to be reversible, in contrast to mutations. Modulating dietary intake of folate and methionine as components of the one-carbon metabolism pathway may have implications for breast cancer development and progression. As breast cancer incidence continues to rise among Asian women, further research exploring the interactions between nutrition and epigenetics is expected to advance breast cancer prevention and treatment.

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Author Contributions

YA designed the study and wrote the manuscript. GH contributed to the section "Epigenetics in Cancer"; SM contributed to the section "One-Carbon Metabolism and Epigenetics"; and RA contributed to the section "Methyl-Group Donors and Breast Cancer risk". All authors approved the final version of the manuscript.

Conflicts of Interest

The authors have declared that they have no potential conflicts of interest.

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