Association of Intake Folate and Related Gene Polymorphisms with Breast Cancer

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Summary Breast cancer is one of the most common malignancies in women worldwide and is associated with a variety of risk factors. Folate and vitamin B12 are key elements of the one-carbon metabolism pathway where methylenetetrahydrofolate reductase (MTHFR) plays a significant role. Though many molecular and epidemiological studies have been performed to explore the relationship between intake folate, vitamin B12, MTHFR gene polymorphism and breast cancer risk, there is no consensus to date. By reviewing the relevant literatures and summarizing the potential effect of dietary folate intake on MTHFR genes polymorphism and breast cancer risk, we conclude that MTHFR C677T gene polymorphism is associated with breast cancer risk among Asian, but not Caucasians, and the MTHFR A1298C gene polymorphism is not a susceptibility factor of breast cancers. Concomitant low activity of MTHFR enzyme resulted from C677T gene polymorphism and low dietary folate intake is associated with increased breast cancer risk.

Key Words vitamin B9, MTHFR genes polymorphism, one-carbon metabolism pathway, DNA methylation, malignancies

Background The interrelationship among genetics, metabolic needs and dietary adequacy is a topic of intense interest in the area of folate nutrition. Incidence of breast cancer is increasing around the world and it is still the leading cause of cancer mortality in women. About 235,303 new cases of breast cancer and approximately 40,430 deaths per year have been reported in the United States (1). The incidence of breast cancer is increasing in developing countries with a rate of 3% to 4% (2). The etiology of breast cancer is still not fully understood. Population studies suggest that genetic factors, including gene polymorphisms and the presence of mutations might be strong risk factors that influence the individual differences in breast cancer susceptibility (3). Epidemiological studies have demonstrated an association between folate deficiency and an increased risk of a variety of cancers (4). The factors associated with the increased breast cancer risk include not only genetic mutations and lifestyle, but also nutritional status. However, folate is plentiful in vegetables and fruits while vitamin B12 is manly stored in animal food. All these vitamins have been confirmed with reduced risk of several cancers. The crucial role of folate as the donor of one-carbon groups in both DNA methylation and DNA synthesis may explain some of these observations (5). Methylenetetrahydrofolate reductase (MTHFR) is a type of folate-related enzymes (6). Biological functions of folate and vitamin B12 within one-carbon metabolism are to facilitate deoxynucleoside triphosphate synthesis and to provide methyl groups required for intracellular methylation reactions. To date, many molecular, epidemiological studies have been performed to evaluate the association between MTHFR gene polymorphism and different types of cancer risk in diverse populations. Methionine synthase (MTR) is another key enzyme controlling folate metabolism. It catalyzes the remethylation of homocysteine to form methionine with the methyl donated by 5-methyltetrahydrofolate (7). One-carbon metabolism pathway plays a key role in genome integrity, DNA methylation, and gene expression. Any aberration in this pathway might be associated with the risk of breast cancer and its phenotype (8). Mutations in its coding gene can lead to a decrease in the efficiency of purine nucleotide and thymidylate synthesis, as well as to modifications in DNA methylation profiles. However, variants of MTHFR C677T and A1298C are good candidates to study the role of genetic variants of folate metabolizing enzymes in breast cancer risk. The present review summarizes the association of MTHFR C677T and MTHFR A1298C variants with folate and vitamin B12 intake in breast cancer susceptibility to various

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populations.

**Evidence Acquisition**

Relevant studies published before 31 November 2017 was identified by searching PubMed and EMBASE. Searching terms were “intake folate,” “B vitamins” and “breast cancer,” in combination with “methylene-tetrahydrofolate reductase” or “MTHFR” or “polymorphism.” We also hand-checked the reference lists of all the included studies to make sure no study was missed.

**Role of folate in human metabolic processes**

Folate, also known as vitamin B₉, is a water-soluble vitamin and its name is derived from the Latin word folium, which means leaf. Folate is found naturally in green leafy vegetables, cereals, legumes and fruits, while folic acid is the synthetic form of the vitamin. Folate accepts one-carbon units from donor molecules and passes them on via various biosynthetic reactions (9). In their reduced form cellular folates function conjugated to a polyglutamate chain. These folates are a mixture of unsubstituted polyglutamyl tetrahydrofolates and various substituted one-carbon forms of tetrahydrofolate (e.g., 10-formyl, 5,10-methylene, and 5-methyl) (Fig. 1). The reduced forms of the vitamin, particularly the unsubstituted dihydro and tetrahydro forms, are unstable chemically. They are easily split between the C-9 and N-10 bond to yield a substituted pteridine and p-amino-benzoylglutamate, which have no biologic activity (10). Substituting a carbon group at N-5 or N-10 decreases the tendency of the molecule to split; however, the substituted forms are also susceptible to oxidative chemical rearrangements and, consequently, loss of activity. The folate found in food consists of a mixture of reduced folate polyglutamates. However, folic acid is reduced in cells by the enzyme dihydrofolate reductase to the di- and tetrahydro forms. This takes place within the intestinal mucosal cells, and 5-methyltetrahydrofolate is released into the plasma. Functional folates have one-carbon groups derived from several metabolic precursors (e.g., serine, N-formino-L-glutamate, folate, etc.). With 10-formyltetrahydrofolate the formyl group is incorporated sequentially into C-2 and C-8 of the purine ring during its biosynthesis. Likewise the conversion of deoxyuridylate (a precursor to RNA) into thymidylate (a precursor to DNA) is catalyzed by thymidylate synthase, which requires 5,10-methylenetetrahydrofolate. Thus, folate in its reduced and polyglutamylated forms is essential for the DNA biosynthesis cycle shown in Fig. 1. The DNA and methylation cycles both regenerate tetrahydrofolate. However, there is a considerable amount of catabolism of folate and a small loss of folate via excretion from the urine, skin, and bile (11). There is a need to replenish the body’s folate content by uptake from the diet. If there is inadequate dietary folate, the activity of both the DNA and the methylation cycles will be reduced. A decrease in the former will reduce DNA biosynthesis and thereby reduce cell division.

**Association of folate with breast cancer**

Folate is involved in DNA synthesis, repair, and methylation. It has been hypothesized that high intake of folate may reduce the risk of human cancers, including breast cancer. In fact, breast cancer begins in any part of breast, caused by abnormal cells growth and division. Literature revealed that folate metabolism
imbalance may be involved in predisposition to cancer. Folate metabolism pathway regulates the intracellular folate pool for synthesis and methylation of DNA (12). The serum folate enters into tissue cells through folate receptors, and then it was turned into tetrahydrofolate via dihydrofolate reductase. Methylenetetrahydrofolate reductase (MTHFR) then transformed the 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, which supplied a methyl group for transformation of homocysteine to methionine in a reaction catalyzed by methionine synthase (MTR) (13). During the past several decades, many epidemiological studies have been conducted to evaluate the relationship between folate intake or blood folate levels and breast cancer risk (Table 1). A more pronounced inverse association between folate intake and breast cancer risk was observed among women who consumed high levels of folate cofactors (methionine, vitamin B12, and vitamin B6) than those whose intake levels of these nutrients were low (14). However, there is still no consensus on such a relationship. Several studies have suggested that high folate intake or high serum folate level may reduce the risk of breast cancer, especially for those with high alcohol consumption while some other studies found no such associations. Investigators used data from a population based case-control study of breast cancer conducted in urban Shanghai to evaluate the association of dietary folate intake and breast cancer risk, their studies found evidence of a decreased breast cancer risk associated with high folate consumption among women who do not regularly consume alcohol (14). This relationship was especially apparent among subjects who also consumed higher amounts of methionine, vitamin B12, or vitamin B6. One study found that folate intake was related to reduced breast cancer risk only among premenopausal women, whereas an inverse association was observed in postmenopausal women (15), particularly those who drank alcohol regularly. However, only a few studies have examined the association of dietary folate intake with breast cancer risk, and the results from these studies have been inconsistent (16). In addition, inadequate levels of serum folate, vitamin B6, and vitamin B12 have been associated with increased breast cancer risk (17, 18). These vitamins all participate as coenzymes in the synthesis of purines and thymidylate for DNA synthesis. Altered DNA methylation, disruption of DNA integrity, and interference with DNA repair are hypothesized mechanisms by which imbalances in folate and other B vitamins may influence nucleic acid metabolism and participate in carcinogenesis (19). The relation of folate intake with breast cancer risk has been investigated in five large prospective cohorts, most of which have not found an overall association of folate intake and breast cancer risk (15, 16, 20–22). However, in three of these studies, low folate intake seemed to increase breast cancer risk among women with high alcohol intake (15, 16, 22). This apparent contradiction may be explained by differences in folate intake between populations. Few epidemiologic studies have evaluated vitamin B6 and vitamin B12 and breast cancer risk. In addition, the association of micronutrient intake and breast cancer seems to differ by menopausal status and levels of other micronutrients (23, 24). It has been reported that among individuals with prevalence of homozygous TT genotype for the 677CT transition in the MTHFR gene with low folate intake has been associated with more substantial increased breast cancer risk than those with other genotypes (24).

**Association of MTHFR gene polymorphisms with breast cancer**

**MTHFR gene polymorphisms.** Breast cancer is a multifactorial disease involving biological, endocrine factors, reproductive life, behavior and lifestyle. It is the leading cause of women death worldwide due to it metastasis to other organs. Development of human breast cancers is a multistage process, arising from genetic alterations that drive the transformation of normal mammary epithelial cells into highly malignant derivatives. Epidemiological evidence shows that folate deficiency is a breast cancer risk factor (22). MTHFR is a key enzyme in folate metabolism and regulates the intracellular folate pool for DNA synthesis and methylation (Fig. 1) (25). Two common allele variants of the MTHFR gene are C677T and A1298C, the point mutation of C to T and A to C may decrease the activity of enzyme (26). Heterozygous and homozygous carriers of the 677T allele variant reduced the activity of enzyme to 30–40% and 60–70%, respectively (27). The effect of the 1298C allele variant is less severe and homozygous carriers of this allele have a moderate 30–40% reduction of the enzyme activity, yet its function remains controversial (28). Furthermore, people who are heterozygous at both loci, C677T and A1298C, experience an intermediate activity loss of 40–50% (29). It has been shown that the 677T allele variant increases the plasma homocysteine concentration in humans and reduces DNA methylation in cancer patients, which indicates a reduced synthesis of methionine and a more limited availability of the methyl donor, S-adenosyl-methionine, in the presence of low activity T allele (30). Many studies investigated the association between the two genotypes and breast cancer incidence. Although significant associations were observed in some studies, a clear linkage between MTHFR gene polymorphisms and the risk to develop breast cancer has not been established (31). Recently, the two MTHFR genotypes were found to modulate the chemosensitivity of cancer cells to 5-fluorouracil and methotrexate. It was stated that two functional polymorphisms in the MTHFR gene affect the survival of ER-negative breast cancer patients (32). We did not observe significant interactions between the two SNPs and chemotherapy on breast cancer survival but observed interactions with race or ethnicity and alcohol consumption.

**Prospective from meta-analysis and case-control studies.** The gene encoding MTHFR is located in chromosome 1p36.3 and has several polymorphisms, the most common ones are MTHFR C677T and MTHFR A1298C. The point mutation of C to T at nucleotide 677 of the MTHFR gene (Ala222Val, rs1801133) causes an ala-
Table 1. A summary of different observational studies and meta-analysis that correlate folate intake, gene polymorphism and the risk of breast cancer.

| Investigations | Study design | Findings | References |
|----------------|-------------|----------|------------|
| MTHFR polymorphisms and breast cancer risk | Population-based case-control study | Significant association between breast cancer, C677T & A1298C polymorphism exist | (51) |
| Dietary intake of folate, vitamin B2, B6, B12, genetic polymorphism of related enzymes, and risk of breast cancer | A case-control study in Japan | No association between intake of folate, related B vitamins & genotypes of MTHFR/MTR & breast cancer | (70) |
| Dietary folate consumption and breast cancer risk | A case-control study in six Italian areas | No significant association between dietary folate consumption & breast cancer | (71) |
| Dietary folate consumption and breast cancer risk | A case-cohort analysis in Canada | No significant association between dietary folate consumption & breast cancer | (16) |
| A prospective study of folate intake and the risk of breast cancer | Prospective cohort study | Adequate folate intake may reduce breast cancer with excess alcohol consumption | (15) |
| Folate and other one-carbon metabolism–related nutrients and risk of postmenopausal breast cancer | Prospective cohort study | Dietary folate intake may be positively associated with postmenopausal breast cancer | (72) |
| A prospective study on folate, B12, pyridoxal 5′-phosphate (B6) and breast cancer | Nested case-control study | Folate intake may be associated with postmenopausal breast cancer | (17) |
| Folate intake and risk of breast cancer by estrogen and progesterone receptor status | Swedish mammography cohort study | No association between dietary folate intake and risk of total breast cancer | (73) |
| Observational and genetic association studies of folate intakes and breast cancer risk | A meta-analysis | A lack of dietary folate intake is not associated with the risk of breast cancer | (74) |
| Folate intake and the risk of breast cancer | A systematic review & meta-analysis | The meta-analysis of total folate showed no statistically significant association with breast cancer | (75) |
| Dietary folate intake and breast cancer risk | A case-control study in urban Shanghai | Dietary intake of methionine, vitamin B12, and vitamin B6 were not independently related to risk of breast cancer | (14) |
| Methionine synthase A2756G polymorphism and breast cancer risk | A meta-analysis | No significant association between A2756G and breast cancer risk | (76) |
| Association of MTHFR gene polymorphisms with breast cancer survival | A case-control study of African-American & Caucasian | MTHFR SNPs, C677T and A1298C, were associated with breast cancer survival | (32) |
| Association of MTHFR, MTRR and MTR polymorphisms with breast cancer risk | A case-control study in West China | MTHFR rs1801133 and MTRR rs1801394 polymorphisms are potential risk factors for the development of breast cancer | (77) |
| Investigations                                                                 | Study design                        | Findings                                                                                                                                                                                                 | References |
|-------------------------------------------------------------------------------|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Association between MTHFR C677T gene polymorphism with breast cancer         | A case-control study in Iran        | No genetic variation of MTHFR C677T polymorphism is involved in the breast cancer risk in a population of North Iranian patients                                                                         | (78)       |
| Association of MTHFR (C677T) gene polymorphism with breast cancer            | A case-control study in North Indian| Association of the CT genotype and the T allele of the MTHFR (C667T) gene may increase the risk for breast cancer                                                                                       | (79)       |
| Genetic polymorphisms of the methylenetetrahydrofolate reductase gene, plasma folate levels and breast cancer | A case-control study in Taiwan      | The MTHFR 677T and 1,298C variant alleles were associated with decreased risk for breast cancer                                                                                                        | (80)       |
| Methylenetetrahydrofolate reductase gene C677T polymorphism and breast cancer risk | A meta-analysis                     | Modest association between MTHFR C677T polymorphism with breast cancer exists                                                                                                                             | (81)       |
| Methylenetetrahydrofolate reductase polymorphisms and breast cancer          | A case-control study in China       | MTHFR C677T polymorphism was significantly associated with breast cancer risk in the Chinese population                                                                                             | (82)       |
| MTHFR and MTR polymorphisms and breast cancer                               | A case-control study in Brazil      | 677 C>T and 2756 A>G substitution does not appear to influence the risk of breast cancer                                                                                                               | (83)       |
| MTR and MTRR polymorphisms, dietary intake, and breast cancer risk           | A case-control study in urban Shanghai | MTR and MTRR genotypes are not likely to play an important independent role in breast cancer etiology                                                                                                    | (84)       |
| Role of polymorphism of methylenetetrahydrofolatehomocysteine methyltransferase (MTR) A2756G and breast cancer risk | A case-control study in Iran        | There was a significant association of breast cancer risk with MTR 2756 GG and AA polymorphism                                                                                                           | (85)       |
| Association of polymorphisms in one-carbon metabolism genes and postmenopausal breast cancer incidence | A case-control study                | Polymorphisms (SNP) in three different genes were significantly associated with breast cancer                                                                                                           | (86)       |
| One carbon metabolism, MTHFR polymorphisms, and risk of breast cancer        | A case-control study                | The MTHFR 677T variant allele associated with increased risk of breast cancer                                                                                                                          | (36)       |
| One carbon metabolism and breast cancer risk                                 | A case-control study in Germany     | A borderline inverse association was observed between dietary folate & breast cancer risk                                                                                                                  | (43)       |
| Genetic polymorphisms in the one-carbon metabolism pathway and breast cancer risk | Case-control study and meta-analyses | No association was found between dietary folate intake and risk of breast cancer                                                                                                                          | (87)       |
| Folate, vitamin B12 and postmenopausal breast cancer                         | Prospective study of French women   | High intakes of folate & vitamin B12 were independently associated with decreased breast cancer risk                                                                                                      | (88)       |
| Folate and risk of breast cancer                                             | A meta-analysis                     | No clear relationship between folate intake & breast cancer risk was found                                                                                                                             | (89)       |
| Methylenetetrahydrofolate reductase polymorphism and susceptibility to breast cancer | A case-control study                | The low activity C677T genotype of MTHFR may increase the risk of early onset breast cancer                                                                                                           | (35)       |
| Investigations                                                                 | Study design                      | Findings                                                                                           | References |
|------------------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------------------|------------|
| Vegetables, fruits, and related nutrients and risk of breast cancer          | Case-control study in Uruguay     | No evidence for an association between related nutrients, fruits, vegetables & breast cancer       | (90)       |
| Does dietary folate intake modify effect of alcohol consumption on breast cancer risk? | Prospective cohort study          | No direct association was found between dietary folate intake and risk of breast cancer             | (91)       |
| Methylglyoxal dietary intake and risk of breast cancer among African-American women | A case-control study              | High level of alcohol consumption seemed more likely to be related to tumors with un-methylated genes | (92)       |
| MTHFR polymorphisms, diet, HRT, and breast cancer risk                      | Multiethnic cohort study           | Folate intake exhibited no modifying effect on the genotype-breast cancer relationship              | (93)       |
| Folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> intake and the risk of breast cancer among Mexican women | A case-control study              | High intake of folate & vitamin B<sub>12</sub> were independently associated with decreased breast cancer risk | (94)       |
| Plasma folate, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, homocysteine, and risk of breast cancer | A nested case-control study       | Higher plasma levels of folate & vitamin B<sub>6</sub> may reduce the risk of developing breast cancer | (18)       |
| Association between MTHFR gene 1298A>C polymorphism and breast cancer susceptibility | A case-control study              | No significant association between MTHFR gene 1298A>C polymorphism and breast cancer              | (95)       |
| Folate and breast cancer: the role of polymorphisms in methylenetetrahydrofolate reductase (MTHFR) | A case-control study              | No association between the MTHFR A1298C polymorphism and breast cancer risk                       | (31)       |
| Methylenetetrahydrofolate reductase A1298C polymorphism and breast cancer risk | A case-control study              | No association between the MTHFR A1298C polymorphism and breast cancer risk                       | (96)       |
| Methylenetetrahydrofolate reductase gene and susceptibility to breast cancer | A case-control study              | A significant association between MTHFR C677T polymorphism & risk of breast cancer exists in pre-menopausal women | (97)       |
| Methylenetetrahydrofolate reductase polymorphism, diet, and breast cancer in Korean women | A case-control study              | MTHFR polymorphism did not influence individual susceptibility to breast cancer                    | (98)       |
| Polymorphisms of one-carbon metabolizing genes and risk of breast cancer      | Population based study            | No significant association between A2756G and breast cancer risk                                    | (99)       |
| One-carbon metabolism and breast cancer                                       | An epidemiological perspective    | No evidence of DNA methylation by one-carbon metabolism & risk of breast cancer                    | (100)      |
| The methylenetetrahydrofolate reductase C677T polymorphism and breast cancer risk in Asian populations | A case-control study              | A significant association between MTHFR C677T polymorphism & risk of breast cancer exists           | (61)       |
nine to valine change at position 222 of the polypeptide that result in a thermolabile enzyme with reduced catalytic activity (33). Each copy of the 677T allele results in a 35% decreased MTHFR activity. In homozygous genotype of MTHFR 677TT, the MTHFR enzyme has 30% full activity. However, in the presence of heterozygous genotype of MTHFR 677CT, the activity of enzyme is 65% (34). There are controversial reports related to the role of MTHFR C677T variants in susceptibility to breast cancer in various populations (Table 1 and Table 2). Studies found an association between the increased risk of breast cancer with MTHFR C677T polymorphism in population of England, Mexican, south-eastern European women, and in population of Swedish and Brazilian post-menopausal women (35–41). In contrast, in a large sample of Canadian, Spanish, German and West Siberian Region of Russia women, the MTHFR C677T was not a risk factor for breast cancer (42–45). There are several studies from Asian populations reporting the influence of MTHFR C677T variants in breast cancer susceptibility, but also with inconsistency. It seems that the MTHFR 677TT genotype was associated with breast cancer in Chinese, Iranians, Jordanian, Turkish, Kazakh, Indian & East Asian population. However, the meta-analysis did not find such association in Caucasian population (59, 60). The latter meta-analysis suggested the risk of breast cancer was significantly associated with postmenopausal status (60). Also, two recent meta-analyses suggested a significant relation between MTHFR C677T genotype and breast cancer risk in Asian populations (61, 62). The association of MTHFR C677T polymorphism with hypomethylation of DNA might suggest a role for this polymorphism in the development of cancer. According to the literature, it seems that MTHFR C677T is associated with breast cancer risk among Asian populations, especially East Asians, but not in Caucasian populations. The inconsistent findings of association between the MTHFR C677T in various populations may underlie differences in ethnicity, lifestyle, and disease prevalence as well as possible limitations due to the relatively small sample size. There are a wide variation in the T allele frequencies of control resources in Asians (0.396), Indians (0.132), Caucasians (0.326), Middle Eastern countries (0.201), and Africans (0.196) that might account for the discrepancy in association between the MTHFR C677T polymorphism and cancer risk in different ethnic groups (62).

### Association of DNA methylation with breast cancer

Diets deficient in methyl group donors (choline, folate, methionine, and vitamin B12) are associated with spontaneous and chemically induced development of hepatocellular carcinoma in rats (63). Folate, in the form of 5-methyltetrahydrofolate, is involved in remethylation of homocysteine to methionine, which is a precursor of S-adenosylmethionine (SAM), the primary methyl group donor for most biological methylations including that of DNA (Fig. 1). After transferring the methyl group, SAM is converted to S-adenosylhomocysteine (SAH), a potent inhibitor of most S-adenosylhomocysteine (SAH), a potent inhibitor of most S-adenosylmethionine-dependent methyltransferases (64). Cravo et al. firstly proposed that a mechanism by which folate deficiency enhances carcinogenesis might be through an induction of genomic DNA hypomethylation based on the biochemical function of folate in mediating one-carbon transfer and on evidence from animal experiments that demonstrated methyl group donor deficiency-induced DNA hypomethylation (65). Thus, several human studies have investigated the correlations between DNA methylation and folate status. In human subjects with normal folate status, no significant correlations between genomic lymphocyte DNA methylation and RBC folate and plasma homocysteine concentrations were observed (66). Therefore, DNA hypomethylation was proposed as one of the possible mechanisms for the development of hepatocellular carcinoma associated with methyl-deficient diets (67). Furthermore, there is evidence that folate status influ-

### Table 2. Related methylene tetrahydrofolate reductase C677T polymorphism and breast cancer in various populations.

| Population | Findings | Reference |
|------------|----------|-----------|
| Chinese, Iranian, American, European, Mexican, Jordanian, Turkish, Kazakh, Indian & East Asian | Association with breast cancer risk | (40, 41, 48, 51, 52, 55–60, 62, 101) |
| Turkish & British | Association with pre-menopausal breast cancer risk | (35, 46, 47) |
| Swedish, Japanese, Brazilian & East Asian | Association with post-menopausal breast cancer | (37, 39, 49) |
| Caucasians, Canadian, Spanish, German & Russian | Lack of association with the risk of breast cancer | (38, 42–45, 59, 60) |
quences DNA methylation through an interaction with the MTHFR C677T polymorphism (5). MTHFR is a critical enzyme in folate metabolism that catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, thereby playing an important role in DNA synthesis, maintenance of nucleotide pool balance, and DNA methylation (Fig. 1). Christensen et al. examined a cohort of women with breast cancer and the DNA methylation level at 1413 sites in 733 genes (68). They found that dietary folate intake was associated with DNA methylation class membership in primary breast tumors. Genomic DNA methylation in peripheral blood mononuclear cells was recently shown to directly correlate with folate status and inversely correlate with plasma homocysteine levels. MTHFR TT genotypes had a diminished level of genomic DNA methylation compared with those with the CC wild-type (69). When analyzed according to folate status, however, only the TT subjects with low levels of folate accounted for the diminished genomic DNA methylation.

Conclusion

Folate and MTHFR gene are key elements of the one-carbon metabolism pathway which are significantly associated with breast cancers. The association between folate and breast cancer risk largely rely on MTHFR gene polymorphism. MTHFR C677T is associated with breast cancer risk among Asians but not Caucasians, and MTHFR A1298C is not a susceptibility factor of breast cancer. Lower activity of MTHFR enzyme in the presence of C677T allele and low dietary folate intake may result in uracil disincorporation in DNA and breast cancer development. As vitamin absorption and utilization efficiency vary considerably in different populations. Further studies on relationship between serum folate and MTHFR gene polymorphism with breast cancers should be conducted.

Disclosure of state of COI

No potential conflicts of interest were disclosed.

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