Review Article

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Folic acid, one-carbon metabolism & childhood cancer

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Folate has been studied in relation to many diseases, especially cancer. Although it has been postulated to exert a dual effect on development of cancer, its role remains to be clearly defined. Its effect on cancer is the result of gene-nutrient interaction between the genes in folate metabolic pathway and dietary folate availability; mutations in genes of folate metabolism have been shown to alter individual susceptibility to certain childhood cancers as well as response to cancer chemotherapy. Although mandatory fortification of food items with folate has been initiated in some countries, many countries are yet to adopt this due to concerns about undesired adverse effects of high folate levels on health, especially cancer. However, initial reports suggest that folate fortification has led to reduction in incidence of certain childhood cancers such as neuroblastoma, wilms tumour and leukaemias. Despite studies showing folate depletion during antifolate chemotherapy and higher toxicity of chemotherapy in folate-depleted individuals, folate supplementation during cancer chemotherapy is not routinely recommended. Studies investigating the precise effect of folate supplementation during chemotherapy on both short- and long-term outcomes of cancer are needed to arrive at a consensus guideline.

Key words Bioavailability - childhood cancer - dietary sources - folic acid - MTHFR polymorphism - one-carbon metabolism

Introduction

Since its discovery in the 1940s, the importance of folic acid in health and disease is being increasingly recognized. Folate is essential for cell multiplication and homoeostasis due to the role of folate-containing coenzymes in nucleic acid synthesis, methionine regeneration and shuttling; oxidation and reduction of one-carbon compounds are essential for cellular metabolism. Progress in basic, translational and clinical sciences has led to unfolding of knowledge about the complex relationship between folic acid, genes encoding various enzymes related to folate metabolism and cancer[1,2]. The present review aims to address the importance of folates in childhood cancers, including their association with the genes in folate metabolic pathway and the proposed role of folates in carcinogenesis as also the effect of folic acid fortification of food on paediatric cancer epidemiology. It also covers in short the sources, bioavailability, absorption and metabolism of folates along with the clinical aspects of folate deficiency.

Folic acid - historical perspective

The correction of macrocytic anaemia in pregnant women in Bombay[3] (now Mumbai) by yeast extract

prompted the discovery of a new nutrient which was finally extracted from spinach in 1941[4] and named as folic acid. Pure crystalline form of folic acid was synthesized in 1943 combining a pteridine ring, paraminobenzoic acid and glutamic acid together named as 'pteroylglutamic acid'[5]. The term 'folates' refers to a large group of compounds including natural folates and folic acid which take part in one-carbon metabolism. The term 'folic acid' is in turn used to denote the fully oxidized compound which is hardly ever found in natural food items. Soon after its discovery, folic acid was observed to enhance the growth of cancer leading to the use of folate antagonist 4-aminopteroyl glutamic acid (aminopterin) in the treatment of childhood acute lymphoblastic leukaemia (ALL), thus establishing the link between folate metabolism and cancer for the first time[6]. Later in the 1990s, the inverse relationship between colon cancer incidence and folate intake was shown in clinical studies[7]. The beneficial role of folate fortification of food on the incidence of certain childhood cancers has also been reported[8].

Dietary sources and bioavailability of folate

Folates are present in a wide variety of food items, though in a relatively low density, except in the liver[9]. Diets containing adequate amounts of fresh green vegetables are good folate sources[10]. Important food sources according to their folate content are shown in Table I. Although folate content is high in foods from animal sources, but cereals, pulses and green leafy vegetables (GLVs) constitute the major sources in vegetarian diets[11].

The bioavailability of folic acid is determined mainly by two factors, dietary source of folates and host factors which are discussed below:

Food sources

Bioavailability of folates depends on pre-consumption processing of food and food products. Although folates from animal sources (*e.g.* beef) have been found to be stable even after prolonged cooking, the method and duration of cooking have marked effects on the folate retention of green vegetables. Accurate estimation of dietary folate availability is still a challenge, and studies designed to investigate the impact of different cooking methods and duration on folate content of food are limited[12].

Table I. Various common diets according to their folate content

Folate content (µg/100g wt)	Food sources
Rich sources (100-350)	Hen eggs, goat liver, yolks, spinach, soybean (raw), strawberry, Bengal gram, green gram
Good sources (56-83)	Broccoli (raw), soybean (boiled), lentils (raw), potato, banana
Moderate sources (15-30)	White breads, onions, tomato

Source: Refs 10,11

Host factors

Intestinal folic acid absorption occurs through a carrier-mediated process in the proximal small intestine which acts optimally at low pH. Genetic association studies have identified an intestinal folate transporter called the human proton-coupled folate transporter (SLC46A1). Mutations leading to loss of function of this transporter were associated with hereditary folate malabsorption[13]. Other diseases causing malabsorption including coeliac disease, Crohn's disease and ulcerative colitis were also found to be commonly associated with impaired folate absorption[14].

Folate absorption and metabolism

After ingestion, many labile forms of folate get destroyed in the acidic environment of stomach in the absence of protective factors such as ascorbic acid or thiols. The dietary folate which is mostly in the form of polyglutamate has to be reduced to absorbable monoglutamates, a reaction catalyzed by folate conjugase, a rate limiting step in folate absorption. Passive diffusion of folates also occurs in the intestine but only with very high doses[15]. Majority of folate is absorbed in the duodenum and jejunum and a small amount from the colon. The absorbed monoglutamates are taken up by the liver and reconverted to polyglutamates for storage in the liver itself or release into the blood. Liver stores about half of the total body folate, a part of which is secreted into the bile and undergoes enterohepatic circulation. Most of this is reabsorbed, 'supposedly to moderate between-meal fluctuations' in serum folate levels[16]. In the plasma, folate is bound primarily to albumin and transported to the cells through a number of folate transport systems[11].

Folate in one-carbon metabolism and its genetic regulation

A simplified account of folate metabolism, its role in nucleotide (purine/pyrimidine) synthesis, conversion of homocysteine to methionine and methylation of DNA is shown in Fig. 1. The relationship between folate levels and risk of cancer and response to chemotherapy

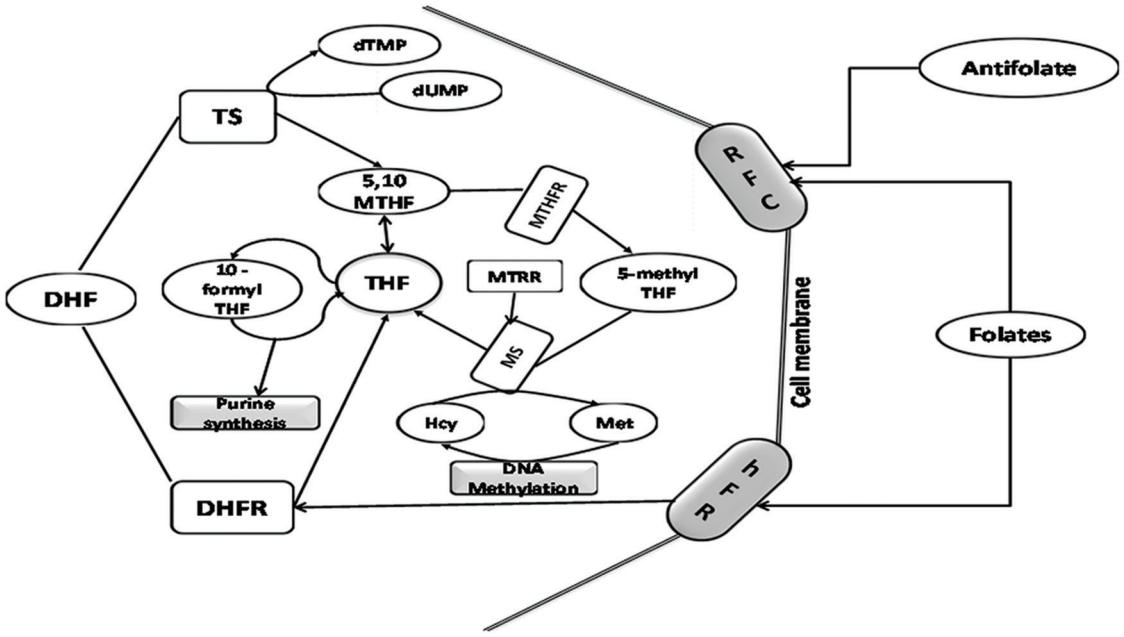

Fig. 1. Simplified scheme for one-carbon metabolism. THF, tetrahydrofolate; DHF, dihydrofolate; RFC, reduced folate carrier; hFR, human folate receptor; MTHFR, 5,10-methylenetetrahydrofolate reductase; DHFR, dihydrofolate reductase; Met, methionine; Hcy, homocysteine; SHMT, serine-hydroxy-methyltransferase; MS, methionine synthase; TS, thymidylate synthase; MT, methyltransferases (enzymes of this pathway are depicted as unshaded boxes, substrates are shown in unshaded ovoid shapes whereas shaded boxes represent biosynthetic/biochemical pathways and shaded cylinders stand for membrane receptors/transporters).

is variably modified by the polymorphisms in key folate metabolizing enzymes.

Alteration in folate metabolism can occur due to altered activity/availability of folate pathway enzymes, which in turn depends on the polymorphisms in their coding genes. These polymorphisms result in decreased folate availability at the site of reaction, leading to hyperhomocysteinaemia and modulate the risk of certain cancers[17] through epigenetic influences such as DNA methylation, uracil misincorporation and altered purine synthesis (vide section on folate and carcinogenesis). The toxicity of antifolate agents used in the treatment of cancer is also influenced by the alteration of genes encoding the proteins of the folate pathway, namely the carrier protein reduced folate carrier (RFC) and enzymes such as thymidylate synthase (TS), 5,10-methylenetetrahydrofolate reductase (MTHFR), methionine synthase reductase (MTRR) and methionine synthase (MS)[17-21].

Reduced folate carrier (RFC)

Folate being a water soluble vitamin is highly lipophobic and hardly crosses the plasma membrane by passive diffusion[22]. Reduced-folate carrier (RFC; additionally known as RFC-1, FOLT, RFT-1 or SLC19A1) is a 60 KDa transport protein with 12 membrane-spanning domains involved in transportation of reduced folates as well as classical antifolates such as methotrexate (MTX) into the cell[23,24]. RFC is located in brush-border membrane of small intestine, colon, basolateral membrane of the renal tubular epithelium, hepatocytes and the retinal pigment epithelium[25].

Loss of RFC expression or function may have important implications in cancer biology, including response to antifolates[24]. Among nearly seven single-nucleotide polymorphisms (SNPs) in its encoding gene, only 80G→A translocation is significant as it causes amino acid sequence alteration, whereas others are silent[26]. This polymorphism alone or in combination with others in the folate pathway may significantly alter folate and homocysteine status[27]. Reduced expression of RFC has been associated with inferior outcome in childhood ALL probably due to intrinsic MTX resistance in these children[28,29].

Thymidylate synthase (TS)

TS, catalyzing the methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), is one of the key enzymes in the *de novo* synthesis of dTMP, an essential precursor of DNA[30]. Being a rate limiting step in DNA synthesis, it has been used as a potential target of many anticancer drugs.

The promoter enhancer region of the *TS* gene contains polymorphism of a double (2R) or triple (3R) 28-base pairs (bp) tandem repeat[31]. The triple repeat results in increased *TS* gene expression, whereas the double repeat is associated with decreased *TS* gene expression. Increased synthesis of dTMP due to higher expression of TS enzyme reduces rate of uracil misincorporation, thereby protecting against oncogenesis[31]. The 3R polymorphism of the promoter region has been shown to be protective for adult ALL and lymphoma[32,33] and improves the outcome of ALL in children[34], whereas the 2R polymorphism has been associated with poor outcome in childhood ALL[34].

5,10-methylenetetrahydrofolate reductase (MTHFR)

MTHFR, one of the most well-studied enzymes in the folate pathway, is a 77 kDa protein encoded by a gene located on the short arm of chromosome 1 (1p36.3)[35]. It catalyzes the step producing 5-methyltetrahydrofolate (5-MTHF), the circulating form of folic acid which is also a methyl donor for the conversion of homocysteine to methionine[36] (Fig. 1). Methionine, when converted back to homocysteine, causes methylation of DNA. SNPs in the *MTHFR* gene lead to alteration in enzyme activity by affecting its thermal stability or affinity towards coenzyme, thereby reducing 5-MTHF production. Although many SNPs in the *MTHFR* gene have been described, till date two of these (at loci 677 and 1298) have been found to be of clinical significance[36].

C677T polymorphism

A common variant of *MTHFR* involves a cytosine (C) to thymine (T) transition at position 677 within exon 4 of the gene, resulting in an alanine to valine amino acid substitution in the protein, reducing MTHFR enzyme activity to 65 and 30 per cent of the CC genotype in the CT heterozygote and TT homozygote variants, respectively[37]. Similar findings have also been documented in a meta-analysis where folate levels were found to significantly differ across 677 genotypes (CC>CT>TT), the difference being most significant between the wild-mutant (CC) and homozygous-mutant (TT) variants[38]. This untoward effect of a mutated genotype can be circumvented by adequate dietary folate[39]. However, in the absence of sufficient folic acid availability, intracellular homocysteine accumulates, methionine resynthesis is decreased and essential methylation reactions are hampered[40].

A1298C polymorphism

An A-to-C transition at locus 1298 within exon 7 results in a change from amino acid glutamate to alanine, reducing MTHFR activity to approximately 60 per cent of the wild state in the homozygous mutated state. The effect of polymorphism at 1298 locus is less pronounced than that at the 677 locus. The enzyme activity is further reduced in the compound heterozygote state (677CT and 1298AC) than in either of the two mutations alone[41,42].

MTHFR gene variants have been proposed to modulate risk of childhood cancer. Most of the case-control studies investigating the association between *MTHFR* polymorphisms and childhood ALL have reported protective effect of 677T allele[43,44] whereas some of these reported no effect[45] and some showed increased risk[46]. 1298C allele was however, not found to have any effect on the risk of childhood ALL[42,46], except in a few studies which reported reduced risk[45]. These disagreements have been attributed to lack of adequate power[47] of the individual studies due to inadequate sample size. In an attempt to circumvent this problem, many meta-analyses[47-54] have been performed (Table II). Though most of these meta-analyses reported a protective effect of 677T variant on childhood ALL, it was significant in only three of these[50,52,54]. When the studies were grouped according to the local folate fortification guidelines, the protective effect was only seen in population covered under mandatory food fortification by folic acid further highlighting the importance of gene-environment interaction, where availability of folic acid enhances the benefit of a favourable genotype[54]. Conversely, the 1298C variant was not seen to alter the risk of childhood ALL in all these meta-analyses except two which showed it to marginally increase the risk[50,54] (Table II).

The protection conferred by 677T allele may be due to inhibition of hypermethylation of CpG islands leading to increased expression of certain tumour suppressor genes conferring protection against leukemogenesis[54]. The lack of association between 1298C and risk of childhood ALL may be largely due to the less significant effect of this polymorphism on the MTHFR enzyme level[54].

5,10-methylenetetrahydrofolate reductase *(MTHFR)* polymorphisms, outcome and toxicity of cancer chemotherapy

Polymorphisms in *MTHFR* (C677T and T677T) have been reported to increase relapse rate of childhood ALL when controlled for other risk factors[55]. *MTHFR*677TT genotype has been associated with higher MTX toxicity as compared to others[56]. Children having genotypes with

Table II. Summary of recent meta-analyses of case-control studies determining association between 5,10-methylenetetrahydrofolate reductase genotype and risk of childhood acute lymphoblastic leukaemia

Study	Year	Number of studies included	Cases: controls		OR (95% CI)	
			C677T	A1298C	C677T	A1298C
Pereira *et al*[48]	2006	8 and 7†	1914:2980	1710:2712	0.88 (0.73-1.06)	0.80 (0.56-1.16)
Wang *et al*[49]	2010	21	3358:6961	-	0.90 (0.88-1.04)	-
Vijayakrishnan *et al*[53]	2010	1715†	2770:4713	2496:4403	0.87§ (0.73-1.03) 0.87ǂ (0.73-1.03)	1.07‡ (0.96-1.20) 1.05§ (0.88-1.25)
Tong *et al*[50]	2011	28	4240:9289	4182:8569	0.81*,¥ (0.71-0.92)	1.16**,‡ (1.01-1.33) 1.16**,∞ (1.00-1.34)
Zintzaras *et al*[51]	2012	23	4517:7117	4360:6717	0.91 (0.82-1.00)	1.04 (0.93-1.16)
Yan *et al*[52]	2012	21	4340:6880	4230:6414	0.83*,¥ (0.72-0.95)	1.02 (0.89-1.17)
Wang *et al*[47]	2012	33	5710:10,798	5356:9906	0.90 (0.82-0.99)	1.01 (0.91-1.11)
Roy Moulik *et al*[54]	2014	3127†	5709:8637	5309:7963	0.90* (0.82-0.99)	1.19** (1.01-1.40)

†Studies on 677 and 1298 polymorphisms, respectively; *Significant risk reduction; **Increase in risk; ¥For TT vs CT/CC; ǂTT vs CC; §CT vs CC; ‡CA vs AA; ∞CA/CC vs AA; §CC vs AA. OR, odds ratio; CI, confidence interval

reduced enzyme activity were found to be at enhanced risk of thrombocytopenia and deranged creatinine in response to high-dose MTX in a study; MTX toxicity was considerably ameliorated when the doses were adjusted depending on *MTHFR* genotype[57]. An increased risk of hepatic, bone marrow, mucocutaneous toxicity with *MTHFR*677CT genotype and a decreased risk of skin toxicity of MTX with *MTHFR*1298AC genotype were also reported in a meta-analysis[58], but these findings did not compare favourably with another meta-analysis[59] which failed to show any role of genotype on the severity of MTX toxicity. Though the adverse effects of *MTHFR* polymorphism on the toxicity of MTX and the outcome of childhood ALL are most likely due to alteration in the folate metabolism, none of these studies accounted for the folate levels of the patients. It is possible that the differences in clinical outcomes could be due to the interaction with other genes as well as nutrients and not the effect of the *MTHFR* genotype alone.

Methionine synthase reductase (MTRR), methionine synthase (MS)

Synthesis of methionine by methylation of homocysteine is mediated by two enzymes MTRR and MS which are located on chromosomes 5p15.3-p15.2 and 1q43, respectively. MS is maintained in its active form by MTRR[60]. The A→G polymorphism at locus 2756 in the protein binding region of *MS* substitutes aspartate with glycine[61]. Polymorphism in this gene may cause elevation of homocysteine, but its significance and effect on folate status are uncertain due to conflicting reports[62,63].

The A66G polymorphism in the *MTRR* gene leads to substitution of isoleucine with methionine at codon 22[60]. Individuals homozygous for the common allele (AA) had higher homocysteine levels compared to those with other genotypes[62,63]; its effect on folate status is also not clear. In adults, *MS* and *MTRR* polymorphisms have been shown to be associated with a reduced risk for ALL[64]; however, paediatric data are lacking[20].

Folate - its dual role in cancer

The role of folate in cancer is paradoxical[65]. Studies, mostly based on laboratory models, show that folate supplementation protects against certain cancers while hastening the progression of some pre-malignant lesions[65,66]. Folate is critically important for cell division because of its role in *de novo* purine and pyrimidine synthesis and also in the DNA repair mechanism. Cancer cells need more substrates for DNA synthesis due to their rapid turnover and thus have higher folate requirement. Folate deficient states or blockade of folate metabolism by antifolates lead to arrest of cell proliferation. Paradoxically, folate supplementation was found to be protective against development of certain cancers due to its crucial role in maintaining the genomic integrity[67]. Folate deficiency may lead to DNA strand breaks, impaired repair, increased mutations and abnormal methylation of DNA, leading to carcinogenesis[66,68]. The proposed paradoxical role of folate in oncogenesis[2,69] is depicted in Fig. 2. Though much light on this issue has been shed by epigenetic studies in animals, extrapolation to human system is subject to usual caveats more so

due to conflicting evidence from randomized studies in human beings[2,70,71].

Folic acid fortification of food - its impact on paediatric cancers

In response to the overwhelming evidence in favour of periconceptional supplementation of folic acid in preventing serious birth defects such as neural tube defect (NTD)[2,72], the United States and Canada initiated mandatory fortification of food products with folic acid from mid-1990s[73,74]. Though this trend was followed by many other countries[75,76], more than 70 per cent of the world population remains uncovered as many countries including those under the European Union opted against fortification due to safety concerns. The concerns were

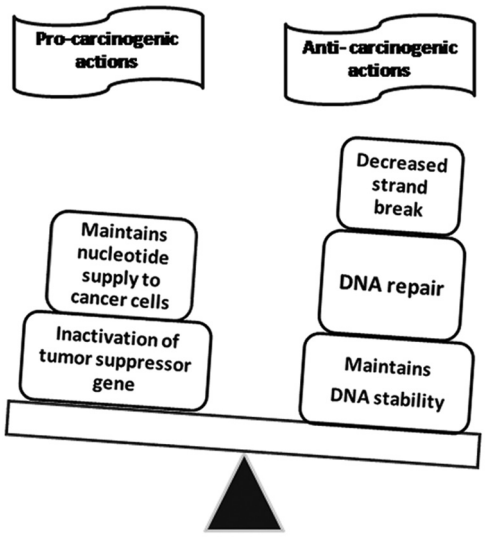

Fig. 2. Proposed dual role of folate in oncogenesis.
Source: Refs 2,69

acceleration of cognitive decline with age and reduction of the efficacy of antifolate drugs such as MTX used in cancer chemotherapy/rheumatic disorders and antiepileptics. The dual role of folates in cancer was another important concern[77]. While being remarkably successful in achieving its primary objective of reducing NTDs by 50 per cent[78], mandatory fortification also provided an opportunity to assess unrelated effects of folates in otherwise healthy population without any ethical concerns. As a sequel to this, many studies were conducted to compare the incidence of childhood cancers between the pre- and post-fortification periods. Even before post-fortification data were available, many case-control studies indicated a possible protective role of maternal supplementation with certain vitamins (mostly vitamins B and folic acid) for childhood cancers such as ALL[77,79], neuroblastoma[78,80], brain tumours[81-83], germ cell tumour[84] and primitive neuroectodermal tumours[83] (Table III). This observation was further strengthened by a meta-analysis, wherein maternal ingestion of prenatal multivitamins was associated with decreased risk for paediatric brain tumours, leukaemia and neuroblastoma, without any specifications as to which component of multivitamins was responsible for this[87]. Another case-control study involving a large number of childhood leukaemia cases documented a protective role of folic acid on childhood leukaemia[86]. A decline in incidence rate ratios of many childhood cancers was demonstrated by a number of studies done in the post-fortification era with inconsistent findings between studies[8,85,88-90] (Table IV). The mechanism through which cancer risk in the offspring is modulated by maternal folic acid supplementation is speculative and is hypothesized to be similar to its role in adult cancers[87] despite the fact that origin of cancer in children

Table III. Studies on association of maternal folate/multivitamin intake and incidence of childhood cancers

Study	Year	Country	Disease	OR (95% CI)
Sarasua and Savitz[79]	1993	USA	ALL	0.50 (0.22-1.13)
			Brain tumour	0.70 (0.26-1.86)
Bunin *et al*[83]	1993	North America	Brain tumour	0.83 (0.45-1.52)
Michalek *et al*[80]	1996	USA	Neuroblastoma	0.38 (0.26-0.55)
Preston-Martin *et al*[81]	1998	North America, Europe, Israel	Brain tumour	0.5 (0.3-0.8)*
Olshan *et al*[78]	2002	North America	Neuroblastoma	0.68 (0.50-0.94)
Wen *et al*[85]	2002	North America, Australia	ALL	0.64 (0.52-0.80)
Milne *et al*[82]	2012	Australia	Brain tumour	0.56 (0.35-0.89)**
Metayer *et al*[86]	2014	Multinational	ALL	0.80 (0.71-0.89)

*In under-5 children whose mothers took supplements for all three trimesters; **Pre-pregnancy folic acid without iron.
ALL, acute lymphoblastic leukaemia; OR, odds ratio; CI, confidence interval

Table IV. Studies comparing the incidence of various paediatric cancers before and after the onset of mandatory food folate fortification in the US and Canada

Study	Year of publication	Years compared	Country	Incidence rate ratios (95% CI)
French *et al*[8]	2003	1985-1997 vs 1998-2000	Canada	
	Neuroblastoma			0.40 (0.25-0.64)*
	Infant ALL			0.97 (0.41-2.27)
	Hepatoblastoma			0.81 (0.35-1.89)
Grupp *et al*[88]	2011	1985-1997 vs 1998-2006	Canada	
	Childhood ALL			1.06 (0.94-1.20)
	Wilms tumour			0.74 (0.57-0.95)*
	Embryonal cancer			0.98 (0.84-1.12)
	Brain tumours			0.95 (0.75-1.19)
Linabery *et al*[90]	2012	1986-1999 vs 1999-2008	USA	
	Lymphoblastic leukaemia			1.02 (0.93-1.12)
	Myeloid leukaemia			1.01 (0.90-1.13)
	Ependymomas			0.70 (0.51-0.97)*
	Astrocytomas			1.10 (0.93-1.31)
	Medulloblastomas			1.10 (0.81-1.49)
	PNET			0.56 (0.37-0.84)*
	Neuroblastoma			0.98 (0.87-1.11)
	Retinoblastoma			0.90 (0.74-1.10)
	Nephroblastoma			0.80 (0.68-0.95)*
	Hepatoblastoma			1.23 (0.91-1.67)
	Rhabdomyosarcoma			0.94 (0.71-1.24)
	GCT			1.05 (0.82-1.36)

*Significant risk reduction in post-fortification period. PNET, primitive neuroectodermal tumour; GCT, germ-cell tumour; ALL, acute lymphoblastic leukaemia; CI, confidence interval

and adults is not identical. This rapidly growing body of knowledge is yet to generate definite evidence in favour of folic acid in the absence of randomized trials in children[87]; though many randomized studies on folate supplementation in adults exist, showing conflicting results[70,71]; therefore, the facts from the post-fortification cohort need to be interpreted with caution before more long-term data are available.

Folates and children on cancer chemotherapy

Folate deficiency is known to manifest as disordered haematopoiesis and bone marrow dysfunction, similar to that produced by the antifolate chemotherapeutic agents in haematological malignancies, by limiting intracellular folate availability and blockade of folate dependent one-carbon metabolism. Thus, MTX forms an important part of chemotherapeutic protocols for childhood ALL and non-Hodgkin's lymphoma[55,56]. Non-antifolate chemotherapeutic agents also cause variable degree of myelosuppression. Bone marrow recovery following chemotherapy is at least partly dependent on the folate status of the patients; therefore, folate supplementation may be an effective intervention to reduce the myelotoxicity of chemotherapeutic agents[91]. However, the idea of recommending folate supplementation to patients on cancer chemotherapy needs exploration as it has not been adequately studied[91] probably due to the concern that folates may interfere with the efficacy of antifolate agents and thus support tumour growth, similar to observations made in studies on clinical response of patients on MTX for rheumatic disorders[92]. Excess of folates may also lead to resistance to antifolates; higher doses of folinic acid rescue following high-dose MTX have also been correlated with increased chances of relapse in paediatric ALL[93].

Though the non-malignant cells are rescued from the toxicity of high-dose MTX by folinic acid, in the absence of any such rescue, the normal cells have to rely on the intrinsic folate status to recover following

lower doses of MTX, which might vary among individuals as well as between populations due to dietary differences as well as differences in folate fortification recommendations across regions. Therefore, promoting folate restriction uniformly to all patients on antifolates needs to be carefully reconsidered. This is more relevant for the developing countries as folate deficiency might be one of the contributors for the higher incidence of toxic deaths during chemotherapy seen in these countries[91]. More studies on this aspect from various regions of the world are warranted to arrive at a proper consensus guideline[91].

Folate status of Indian children with cancer

Though nutritional anaemia is common in Indian children stemming from nutritional deficiencies of iron, folic acid and vitamin B12, Indian data on prevalence of folate deficiency in children are incomplete due to lack of national data or multicentric surveys. Most of the surveys conducted have been limited to children in large cities. In a study on toddlers and preschool children from Delhi, about 15 per cent children were found to be having folate deficiency[94] whereas another study from the same region showed over 40 per cent children between five and 11 yr and nearly one-third of those between 12 and 18 yr to be folate deficient[95]. A study on urban healthy children from southern India found folate deficiency in nearly all the children studied[96].

With the available data on folate deficiency in Indian children, the documented prevalence has been clearly higher than in children from many developed countries such as the USA or European countries according to a review comparing folate and vitamin B12 deficiencies across the globe[97]. Deficiency of folate in healthy Indian children continues to be a common problem due to lack of dietary folate, unlike in developed countries where it has significantly declined after initiation of food fortification.

The data on folate status of Indian children with cancer are also sparse. A case-control study from southern India demonstrated significantly lower levels of folate in children with ALL[98]. Two more studies from north India also showed a high baseline prevalence of folate deficiency in children with newly diagnosed ALL as well as decline in folate levels with chemotherapy[99,100]. Furthermore, folate deficiency in these children was associated with adverse outcome during their initial phases of treatment[99,100].

Future directions

Recent evidence suggests an important role of folates in relation to cancer in both adults and children. Epidemiologic data from countries with mandatory folic acid fortification of food recording decline in incidence of certain paediatric cancers need to be confirmed to generate robust evidence in favour of fortification. Therefore, more epidemiological and basic research is warranted in this field to establish the role of folic acid in cancer prevention, epidemiologically and mechanistically, respectively. In addition, more studies are needed to elucidate the association between folate deficiency and toxicities encountered in children undergoing cancer chemotherapy taking into consideration nutrition and other related confounders. Based on such findings, randomized trials assessing the efficacy and safety of folic acid supplementation in folate deficient children undergoing chemotherapy are needed to generate convincing evidence. This is particularly important for population with high prevalence of folate deficiency as in India where folic acid fortification is not mandatory.

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