Folate, DNA Methylation & Cancer Prevention

Young-In Kim, MD, FRCP(C)
Division of Gastroenterology
Departments of Medicine & Nutritional Sciences
University of Toronto
St. Michael’s Hospital
DNA Methylation

- Heritable, species & tissue-specific postsynthetic modification of mammalian DNA in CpG
- ~ 70% of CpG are methylated
- 3 – 4% of all cytosines are methylated
- 5mC: 0.75 – 1% of the total number of bases
DNA methyltransferase

\[ --\text{CpG}-- + \text{SAM} \xrightarrow{\text{5-mC glycosylase}} --\text{CpG}-- + \text{SAH} \]

\[ \begin{align*}
\text{Substrates} & \quad \text{Deoxycytidine} + \text{S-adenosyl-L-methionine (SAM)} \\
\text{Products} & \quad \text{5-Methyl-cytidine} + \text{S-adenosyl homocysteine (SAH)}
\end{align*} \]
DNA Methylation

**CpG Islands**
- 500 bp window
- G:C content ≥ 55%
- Obs/Exp freq ≥ 0.65
- ~15 – 20% of total genomic CpG
- CpG-rich promoter regions in ~50% of the genes
- Normally unmethylated
  - transcription
- Normally fully methylated
  - X-chromosome inactivation
  - Silenced alleles of imprinted genes

**CpG in bulk of genome**
- ~80% of all CpG

**CpG underrepresented (5-10% of predicted freq)**
- mC → T

**Normally methylated**
- Correct organization of chromatin in active & inactive states
- Silencing of parasitic sequences (transposons, endogenous retroviruses)
- Inactivation of proto-oncogenes
DNA Methylation Programming

CpG Methylation Pattern

5mC
CpG-island methylation

Genetic & Epigenetic Inheritance
Developmental Stochasticity
Environmental Influences

Birth
E₀
Implantation

Age
DNA Methylation & Cancer

Hypermethylation of CpG islands: Gene silencing

Hypomethylation of gene body & bulk chromatin:
## CpG Promoter Hypermethylation & Associated Gene Silencing in Cancer

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered cell cycle control</td>
<td><em>Rb, p16, p15, p14, p73</em></td>
</tr>
<tr>
<td>Repair of DNA damage</td>
<td><em>MLH1, O6-MGMT, GST-Pi, BRCA1</em></td>
</tr>
<tr>
<td>Apoptosis</td>
<td>DAP kinase, caspase 8, TMS-1</td>
</tr>
<tr>
<td>Tumor-cell invasion or tumor architecture</td>
<td><em>E-cahedrin, VHL, APC, LKB1, TIMP-3, THBS1</em></td>
</tr>
<tr>
<td>Growth-factor response</td>
<td><em>ER, RAR-β, SOCS-1</em></td>
</tr>
</tbody>
</table>
Genomic Hypomethylation & Cancer

- Chromosomal Instability
  - Mitotic recombination – deletions (LOH), translocations
  - Chromosomal rearrangements – aneuploidy
- Loss of imprinting
- Activation of intragenomic endoparasitic DNA (Transposons)
- Gene Up-Regulation (protooncogenes?)
DNA Methylation & Colorectal Cancer

CpG island hypermethylation

Mismatch Repair Genes (MMR)
MLH1, MSH2, PMS1, PMS2, MSH3, MSH6

5q APC
β-catenin

Genomic DNA Hypomethylation

12p K-ras

18q DCC DPC4

17p p53

Colonic Mucosa
Hyperproliferative Colonic Epithelium
Early Adenoma
Inter Adenoma
Late Adenoma
Carcinoma
Metastasis

nutrition, physical activity, tobacco, alcohol, drugs
5mC

CpG-island methylation

Altered histone modification pattern
Epigenetics vs. Genetics in Cancer

Genetics
• All-or-nothing
• Fixed effect
• Abrupt
• Probably not reversible

Epigenetics
• Progressive
• Dose-dependent
• Gradual
• Reversible

Diet, Lifestyle Factors, Environment, Drugs

Cancer

Tumor Marker
Prognostic Marker
Predictor of response
Therapeutic Targets
Epigenetic differences arise during the lifetime of monozygotic twins

Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste||, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling†, Emma Carlsson†, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§
Dietary Factors that May Influence Epigenetics & Cancer Susceptibility

- Arsenic, Cadmium, Zinc, Selenium, Nickel
- Folate, Choline, Methionine, Vitamin B12, Vitamin B6, ETOH
- Phytoestrogens: Coumestrol, Equol, Genistein
- Tea polyphenols (EGCG)
- Sulforaphane (isothiocyanate) – cruciferous vegetables (broccoli, broccoli sprouts)
Chemical Structures of Folic Acid & Folate

<table>
<thead>
<tr>
<th>Pterin ring</th>
<th>PABA</th>
<th>Glutamate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pteroic acid</td>
<td>Glutamate</td>
<td></td>
</tr>
<tr>
<td>Folic acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[
R = \text{CH}_3 (N^5), \text{CHO (N}^5 \& N^{10}), \text{CH}=\text{NH (N}^5), \text{CH}_2 (N^5 \& N^{10}) \text{ and CH= (N}^5 \& N^{10})
\]
Biological Function of Folate

Deoxyuridine $\xrightarrow{\text{Dihydrofolate}}$ Deoxyuridylate $\xrightarrow{\text{DHFR}}$ THF $\xrightarrow{\text{MTHFR}}$ 5’-methylTHF $\xrightarrow{\text{SAM}}$ DNA methyltransferase $\xrightarrow{\text{CH}_3}$ DNA---CpG--DNA

Thymidylate Synthetase

5’,10’-methyleneTHF $\xrightarrow{10’\text{-formylTHF}}$ THF $\xrightarrow{\text{B12}}$ Methionine synthetase

Methionine $\xrightarrow{\text{Dimethylglycine}}$ Choline $\xrightarrow{\text{Betaine}}$ Homocysteine

DNA---CpG--DNA $\xrightarrow{\text{DNA methyltransferase}}$ SAH $\xrightarrow{\text{Betaine}}$ Choline $\xrightarrow{\text{Dimethylglycine}}$ Methionine

Folic Acid $\xrightarrow{\text{Diet}}$ Methionine $\xrightarrow{\text{B12}}$ Methionine synthetase

DNA Synthesis
Folate Deficiency & Cancer Risk

- Colorectum
- Lung, Oropharynx
- Breast
- Pancreas
- Prostate
- Cervix, Ovary
- Esophagus/Stomach
- Leukemia
- Neuroblastoma
Dual Effects of Folate on Cancer Risk

Double Edged Sword

Normal Tissues

FS

FD

Cancer risk

Predisposes to cancer

Established (Pre)Neoplastic Foci

FS

FD

Tumor growth

Tumor growth
Folate deficiency

↑ risk of neoplastic transformation
↓ progression of ACF to adenoma
↓ progression of adenoma to cancer
↓ progression of cancer

Normal → ACF → Adenoma → Cancer

↓ risk of neoplastic transformation
↑ progression of ACF to adenoma
↑ progression of adenoma to cancer
↑ progression of cancer

Folate supplementation
Effects of Folate on Normal Colonic Epithelial Cells

- **Folate deficiency increases CRC risk**
  - DNA strand breaks
  - Impaired DNA repair
  - Increased mutagenesis
  - Genomic DNA hypomethylation?

- **Folate supplementation decreases CRC risk**
  - DNA stability & integrity
  - Optimal DNA repair
  - Decreased mutagenesis
  - Prevention of aberrant DNA methylation?
Effects of Folate on Colonic (Pre)Neoplastic Cells

- **Folate deficiency inhibits tumor progression**
  - Ineffective DNA synthesis leading to inhibition of tumor growth & progression
  - **Reversal of promoter CpG islands hypermethylation?**

- **Folate supplementation promotes tumor progression**
  - Provision of nucleotide precursors for proliferation & growth of neoplastic cells
  - **De novo methylation of promoter CpG islands of tumor suppressor genes leading to gene inactivation?**
  - Hypermutability of 5mC in CpG?
Folate & DNA Methylation

Deoxyuridine (dU) → Thymidylate Synthase → Thymidylate dTMP → DNA Synthesis

Deoxyuridylate dUMP → 10’-formylTHF

Purine

Dihydrofolate DHFR → THF

5’,10’-methyleneTHF

MTHFR → 5’-methylTHF

Methionine synthase

B12

Homocysteine

Choline

SAM

Folic Acid

Diet

Methionine

Dimethylglycine

Betaine

SAH

DNMT

DNA---CpG--DNA

CH3
# Folate Deficiency → DNA Methylation? (Rodent Liver)

<table>
<thead>
<tr>
<th>Study</th>
<th>FD</th>
<th>Duration (wk)</th>
<th>Species</th>
<th>DNA CH₃</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>Balaghi et al.</td>
<td>Severe</td>
<td>4</td>
<td>Rat</td>
<td>Genomic</td>
<td>20% ↓</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Severe</td>
<td>6</td>
<td>Rat</td>
<td>Genomic</td>
<td>60% ↑</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p53 (ex 6-7)</td>
<td>40% ↓</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Mild</td>
<td>15 &amp; 24</td>
<td>Rat</td>
<td>Genomic</td>
<td>↔</td>
</tr>
<tr>
<td>Song et al.</td>
<td>Mild</td>
<td>5</td>
<td>Mouse</td>
<td>Genomic</td>
<td>56% ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td></td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Le Leu et al.</td>
<td>Mild</td>
<td>13</td>
<td>Rat</td>
<td>Genomic</td>
<td>↔</td>
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<tr>
<td>Davis et al.</td>
<td>Mild</td>
<td>13</td>
<td>Rat</td>
<td>Genomic</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>AOM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DMH</td>
<td></td>
<td></td>
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</table>
**Folate Deficiency → DNA Methylation? (Rat Colon)**

<table>
<thead>
<tr>
<th>Study</th>
<th>FD</th>
<th>Duration (wk)</th>
<th>DNA CH3</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Kim et al.</td>
<td>Mild</td>
<td>15 &amp; 24</td>
<td>Genomic</td>
<td>↔</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>c-myc</td>
<td>↔</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Mild + DMH</td>
<td>20</td>
<td>Genomic</td>
<td>↔</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>p53 (exon 8)</td>
<td>25% ↓</td>
</tr>
<tr>
<td>Le Leu et al.</td>
<td>Mild + AOM</td>
<td>13 &amp; 26</td>
<td>Genomic</td>
<td>↔</td>
</tr>
<tr>
<td>Davis et al.</td>
<td>Mild + DMH</td>
<td>13</td>
<td>Genomic</td>
<td>↔</td>
</tr>
<tr>
<td>Duthie et al.</td>
<td>Mild</td>
<td>10</td>
<td>Genomic</td>
<td>↔</td>
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<tr>
<td>Choi et al.</td>
<td>Mild + Aging</td>
<td>8 &amp; 20</td>
<td>Genomic</td>
<td>↔</td>
</tr>
<tr>
<td>Sohn et al.</td>
<td>Severe</td>
<td>5</td>
<td>Genomic</td>
<td>30% ↑ wk3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>p53 promoter</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p53 ex 6-7</td>
<td>↓ CpG #1 wk5</td>
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</table>
### Folate Deficiency & SAM/SAH

<table>
<thead>
<tr>
<th>Cell</th>
<th>HCT 116</th>
<th>Caco-2</th>
<th>CHO-K1</th>
<th>NIH/3T3</th>
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</thead>
<tbody>
<tr>
<td><strong>Folate Status</strong></td>
<td>↓ ↓ ↓</td>
<td>↓ ↓ ↓</td>
<td>↓ ↓ ↓</td>
<td>↓ ↓ ↓</td>
</tr>
<tr>
<td><strong>SAM</strong></td>
<td>↑ ↑ ↑</td>
<td>↓ ↓ ↓</td>
<td>↓ ↓ ↓</td>
<td>↑ ↑ ↑</td>
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<tr>
<td><strong>SAH</strong></td>
<td>← → ← →</td>
<td>← → ← →</td>
<td>← → ← →</td>
<td>↓ ↓ ↓</td>
</tr>
<tr>
<td><strong>SAM:SAH</strong></td>
<td>↑ ↑ ↑</td>
<td>↓ ↓ ↓</td>
<td>↓ ↓ ↓</td>
<td>↑ ↑ ↑</td>
</tr>
<tr>
<td>Cell</td>
<td>HCT 116</td>
<td>Caco-2</td>
<td>CHO-K1</td>
<td>NIH/3T3</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------</td>
<td>--------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>Genomic DNA Methylation</td>
<td>↔ ↔</td>
<td>↔ ↔</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Satellite DNA Methylation</td>
<td>↔ ↔</td>
<td>↔ ↔</td>
<td>N/A</td>
<td>↓</td>
</tr>
<tr>
<td>MLH1 &amp; p16 Promoter region</td>
<td>↔ ↔</td>
<td>↔ ↔</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>ER Promoter region CH₃’n</td>
<td>CpG#2,10</td>
<td>CpG#2</td>
<td>N/A</td>
<td>N/A</td>
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</tbody>
</table>

NIH/3T3

CHOC

3T3
<table>
<thead>
<tr>
<th>Cell</th>
<th>HCT 116</th>
<th>Caco-2</th>
<th>CHO-K1</th>
<th>NIH/3T3</th>
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</thead>
<tbody>
<tr>
<td>ER protein expression</td>
<td>❯❯</td>
<td>❯❯</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>DNMT 1 mRNA</td>
<td>N/A</td>
<td>❯</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>DNMT/Dnmt 1 protein expression</td>
<td>❯</td>
<td>❯</td>
<td>N/A</td>
<td>❯</td>
</tr>
<tr>
<td>DNMT/Dnmt 3a protein expression</td>
<td>❯</td>
<td>❯</td>
<td>N/A</td>
<td>❯</td>
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<tr>
<td>DNMT Activity</td>
<td>❯❯</td>
<td>❯</td>
<td>❯❯</td>
<td>❯</td>
</tr>
</tbody>
</table>
Log$_2$(R/G)

CpG loci

HCT116

Caco2
Effect of Folate Deficiency on DNA Methylation & DNMT

- Highly Variable & Complex
- Cell & tissue-specific
- Gene-specific (site-specific)
- Stage of transformation-specific
- May cause both hypermethylation & hypomethylation simultaneously
- Associated with down-regulation of DNMT
# Folate Supplementation → DNA Methylation? (Rodent Liver & Colon)

<table>
<thead>
<tr>
<th>Study</th>
<th>FS</th>
<th>Duration (wk)</th>
<th>DNA CH3</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kim et al.</strong></td>
<td>4-20x BDR + DMH</td>
<td>20 (Rat Colon)</td>
<td>Genomic</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>p53</em> (exon 8)</td>
<td>↑ dose-responsive</td>
</tr>
<tr>
<td><strong>Sohn et al.</strong></td>
<td>4x BDR</td>
<td>5 (Rat Colon)</td>
<td>Genomic</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Achon et al.</strong></td>
<td>40x BDR</td>
<td>4 (Rat Liver)</td>
<td>Genomic</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Choi et al.</strong></td>
<td>4x BDR + Aging</td>
<td>8 &amp; 20 (Rat Liver)</td>
<td>Genomic</td>
<td>15-30% ↑</td>
</tr>
<tr>
<td><strong>Keyes et al.</strong></td>
<td>4x BDR + Aging</td>
<td>20 (Mouse Colon)</td>
<td>Genomic</td>
<td>10% ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>p16</em> promoter</td>
<td>30% ↑</td>
</tr>
</tbody>
</table>
Study 1

Weaning

Wk 0: 0
Wk 3: 2
Wk 8: 2
Wk 30: 8

Study 2

Weaning

Wk 0: 2
Wk 3: 0
Wk 8: 2
Wk 30: 8

Study 3

Weaning

Wk 0: 0
Wk 3: 2
Wk 8: 2
Wk 30: 8
Hepatic Global DNA Methylation

* P<0.05

J Nutr 2008; 138: 703
## Effects of Folate Deficiency on DNA Methylation (Human Studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Dose</th>
<th>Duration</th>
<th>DNA</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rampersaud 2000</strong></td>
<td>Women 60-85 yrs</td>
<td>118 µg/d</td>
<td>7 weeks</td>
<td>Lymphocytes, Genomic</td>
<td>10% decrease</td>
</tr>
<tr>
<td><strong>Jacob 1998</strong></td>
<td>Women 49-63 yrs</td>
<td>56-111 µg/d</td>
<td>9 weeks</td>
<td>Lymphocytes, Genomic</td>
<td>120% decrease</td>
</tr>
<tr>
<td>Study</td>
<td>Subjects</td>
<td>Dose</td>
<td>Duration</td>
<td>Endpoint</td>
<td>Effect</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------</td>
<td>-----------</td>
<td>----------</td>
<td>---------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Cravo</td>
<td>CRC or Adenoma</td>
<td>10 mg/d</td>
<td>6 mo</td>
<td>Rectum</td>
<td>93% ↑</td>
</tr>
<tr>
<td>Cravo</td>
<td>Adenoma</td>
<td>5 mg/d</td>
<td>3 mo</td>
<td>Rectum</td>
<td>37% ↑</td>
</tr>
<tr>
<td>Kim</td>
<td>Adenoma</td>
<td>5 mg/d</td>
<td>6 mo</td>
<td>Rectum</td>
<td>57% ↑</td>
</tr>
<tr>
<td>Ingrosso</td>
<td>Uremic ↑Hcy 5mTHF</td>
<td>15 mg/d</td>
<td>8 wk</td>
<td>Lympho</td>
<td>↑ to N</td>
</tr>
<tr>
<td>Pufulete</td>
<td>Adenoma</td>
<td>400 µg/d</td>
<td>10 wk</td>
<td>Rectum</td>
<td>25% ↑</td>
</tr>
</tbody>
</table>
Effect of Intrauterine Exposure to High Folate?
Folic Acid Fortification

◆ **US FDA**
  - All enriched flour, rice, pasta, cornmeal and other grain products contain 140 µg of folic acid per 100 g of products as of **January 1998**
  - To provide on average 100 µg additional folic acid daily (but limit total daily intake < 1 mg/d)

◆ **Canadian National Program**
  - Mandated on **November 1998** to increase folic acid fortification of all flour and some corn and rice products, providing a daily average of 0.1 mg folic acid
Folate status in the US population

- Serum folate (<6.8 nmol/L)
  - ↓ from 16% to 0.5%
- RBC folate (<317 nmol/L)
  - ↓ from 31% to 3%
- Serum folate (>45.3 nmol/L)
  - ↑ from 7% to 38%*
- Plasma Hcyst (≤ 9 µmol/L)
  - 78%

Am J Clin Nutr 2005; 82: 442
Serum Folate Post Fortification

Pfeiffer 2007
Reduction in Neural-Tube Defects after Folic Acid Fortification in Canada


Figure 1. Prevalence of Neural-Tube Defects, According to Diagnostic Category, in Seven Canadian Provinces from 1993 through 2002.

NOS denotes not otherwise specified.
Effects of Maternal FA Supplementation on Cancer Risk

FA Supplementation

- DNA Synthesis
- DNA Methylation
  - Gene-Specific
  - Genomic
- Agouti viable yellow ($A^{vy}/a$) mutant
  - Obese
  - Hyperinsulinemic
  - High mortality
  - Cancer susceptibility
  - Max. ectopic agouti overexpression

- Pseudoagouti $A^{vy}/a$ mice
  - Lean, healthy, longer life span
  - Min. ectopic agouti expression
In Utero Methyl Diet Supplementation: Changing of the Coat Color in Agouti Viable Yellow ($A^{vy}$) Mice

**Table:** Components and their concentrations in MS and HMSZMet diets (per kg)

<table>
<thead>
<tr>
<th>Component</th>
<th>MS (per kg)</th>
<th>HMSZMet (per kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline, g</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Betain, g</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Folic acid, mg</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>B-12, mg</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>L-Met, g</td>
<td></td>
<td>7.5</td>
</tr>
<tr>
<td>Zinc, mg</td>
<td></td>
<td>150</td>
</tr>
</tbody>
</table>

**References:**
- J Nutr 2002; 132: 2393S
In Utero Methyl Diet Supplementation: Unkinking of the Tail in $Axin^{FU}$ Pups

Science 2005; 310: 1761

2 mg Dams

2 mg  5 mg Folic Acid/kg diet

5 mg Dams

AOM carcinogen (15mg/kg BW)
5 + 6 weeks old

3 weeks old

PUPS

Sacrifice at 34 weeks old
Tumor endpoint
CRC Incidence

OR = 0.36 (p=0.003; 95% CI 0.18-0.71)

AACR 2008
Effect of FA on Global DNA Methylation

Maternal Diet Group (mg Folic Acid/kg Diet)

P<0.001 Pup Diet
Dams

Maternal Diet

2 mg FA

5 mg FA

Pups

Day 0

2 mg

Day 21

5 mg FA

2 mg

Weaning n=10 /diet group

Day 50

Analyze TEB and other mammary gland structures
Effect of Maternal FA on TEB

Maternal Diet (mg FA/kg Diet)

Number/mm²

2 5

p<0.05
Folic Acid Fortification & Cancer Risk

- Pediatric Oncology of Group of Ontario
  - captures 95% of all pediatric cancers in Ontario
- Incidence of neuroblastoma in children
  \[ \leq 17 \text{ age} \]
  - 1.57 cases per 10,000 births (01/1985 – 12/1997)
  - 0.62 cases per 10,000 births (01/1998 – 10/2000)
- Adjusted Incidence Rate Ratio = 0.38
  (95% CI, 0.23 – 0.62)

Clin Pharmacol Ther 2003; 74: 288
Hypothesis

A Temporal Association between Folic Acid Fortification and an Increase in Colorectal Cancer Rates May Be Illuminating Important Biological Principles: A Hypothesis

Mason JB, et al. 2007
The excess incidence of CRC in the US & Canada compared w/ prefortification trends
Folic Acid Fortification & Cancer Risk?

- May prevent the development of new cancers
- May promote the progression of existing (pre)neoplastic lesions
- Effects on epigenetics of the offspring?
- What is the safe and effective range of fortification?
- Generalized mandatory vs. targeted fortification? (NTD vs. CRC prevalence)
Intraepithelial Neoplasia (ACF → adenoma)
Science, medicine, and the future

Is folic acid the ultimate functional food component for disease prevention?

Mark Lucock

BMJ 2004; 328: 211-214
Folic acid — vitamin and panacea or time bomb?

Mark Lucock and Zoë Yates
Nutrition & Epigenetics

- Potentially modifiable by environmental factors including diet
- Maternal & early childhood nutrition during the epigenetically susceptible period may have a profound effect on epigenetics and human diseases including colon cancer
- Potential adverse effects of folic acid fortification on epigenetics → cancer risk
- Nutrition in aging may also have a profound effect on epigenetics and age-related human diseases including cancer
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