Nutrition, epigenetics and health

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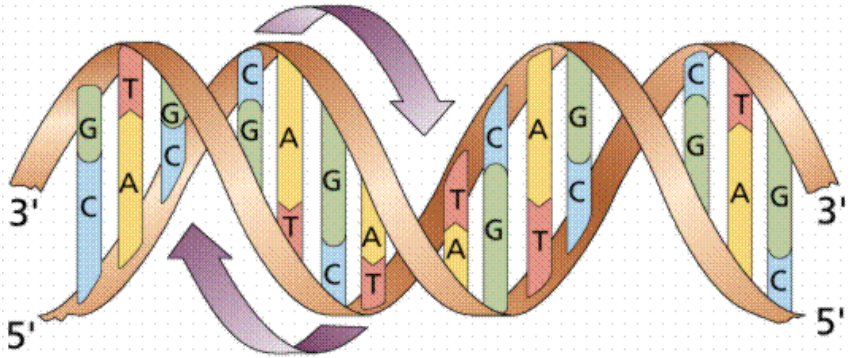
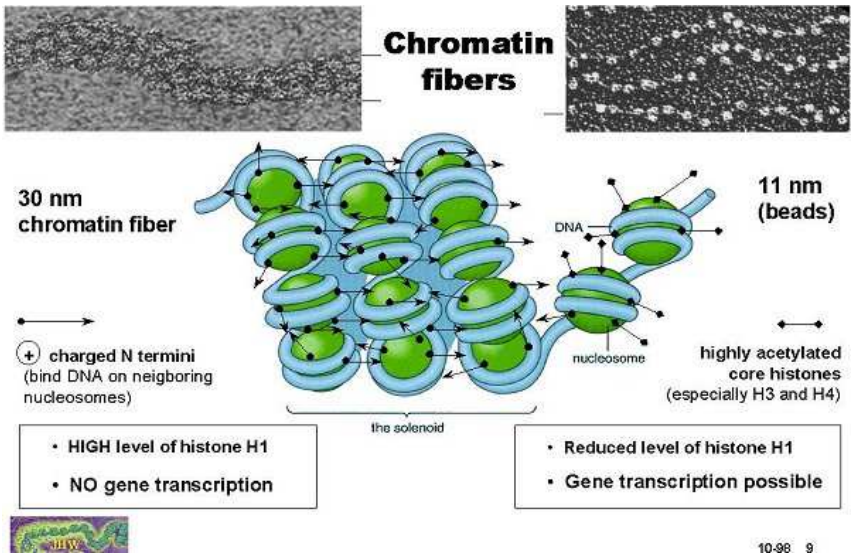
Content

- Introduction to epigenetics
- Epigenetics in chronic diseases and ageing
- The impact of diet and lifestyle on the epigenome
- Summary and future

Genetics vs epigenetics



Genetics - sequence

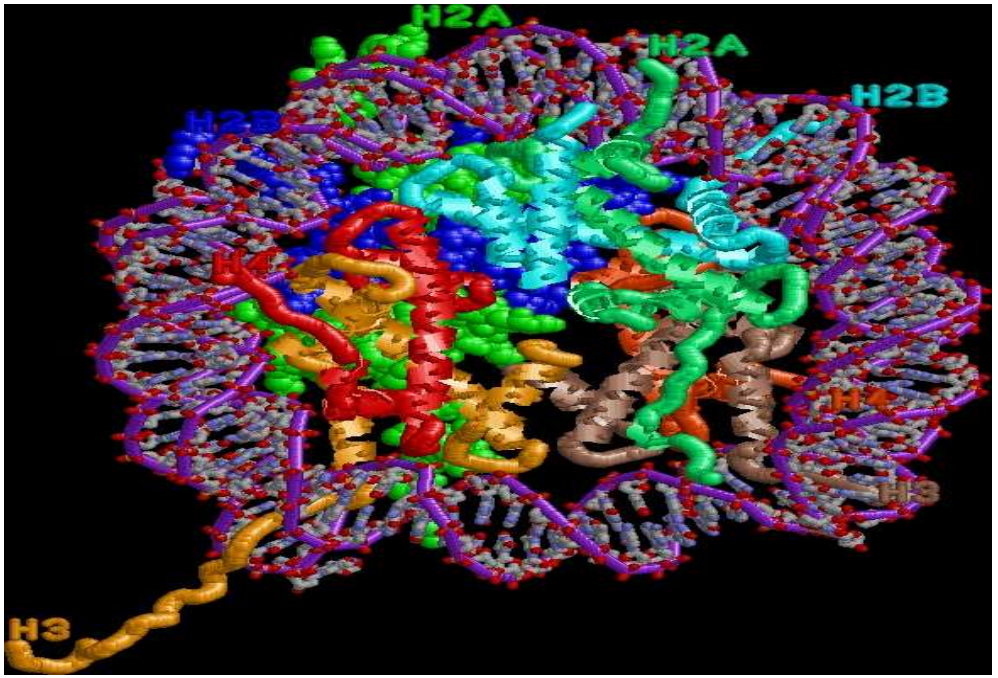


Epigenetics – “outside” sequence

Modifications to DNA or chromatin that affect the higher order structure (“packaging”).

Epigenetic modifications

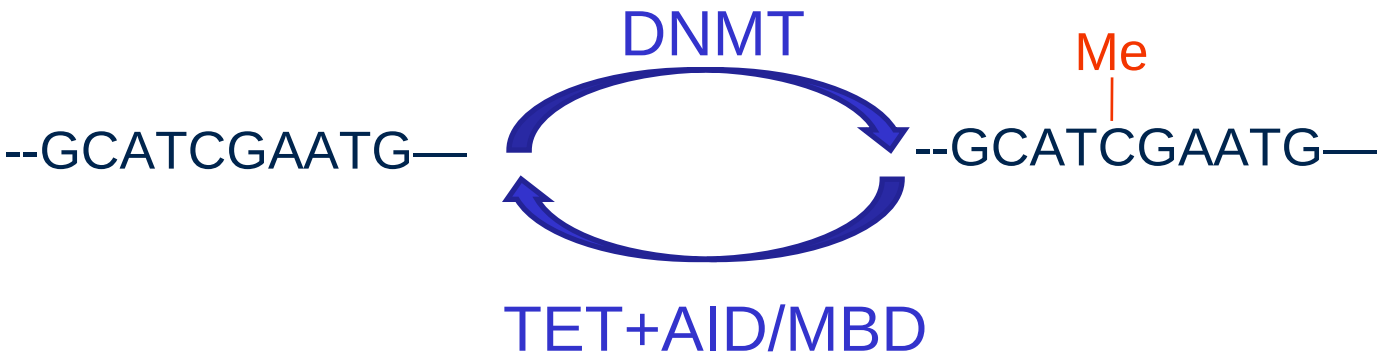
- **Histone modifications - the histone code**
  - Acetylation, methylation, ubiquitylation, phosphorylation, etc



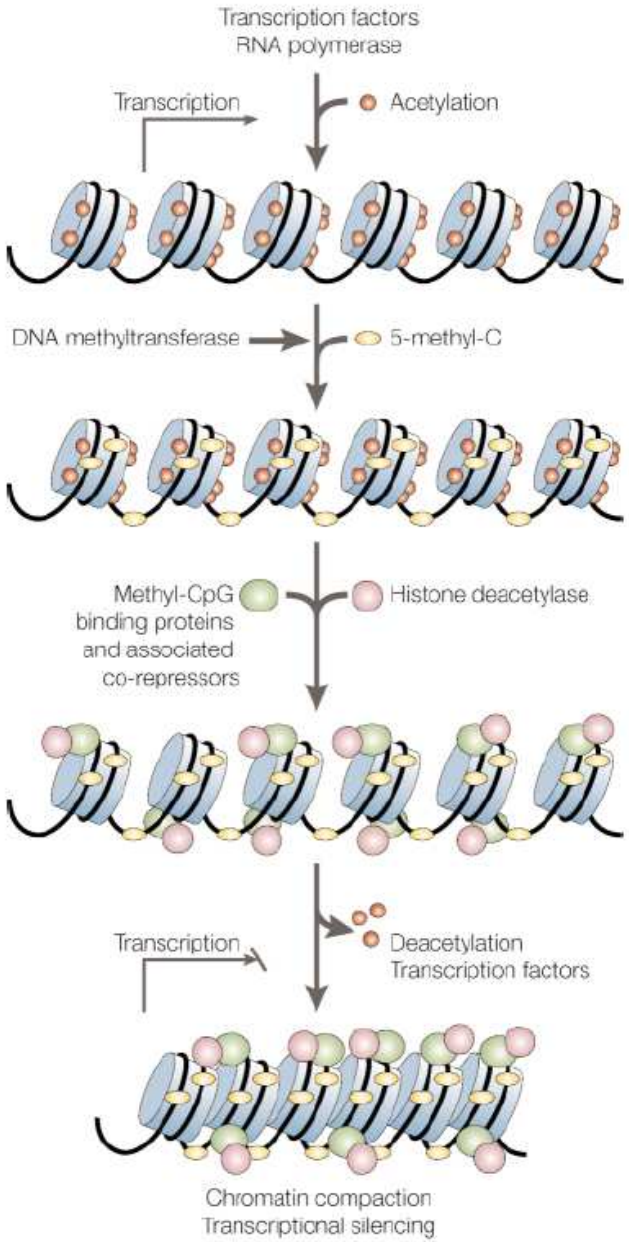
- **DNA methylation**

DNA methylation

- **Enzyme-mediated methylation of cytosines only in CpG dinucleotides**



DNA methylation affects chromatin structure



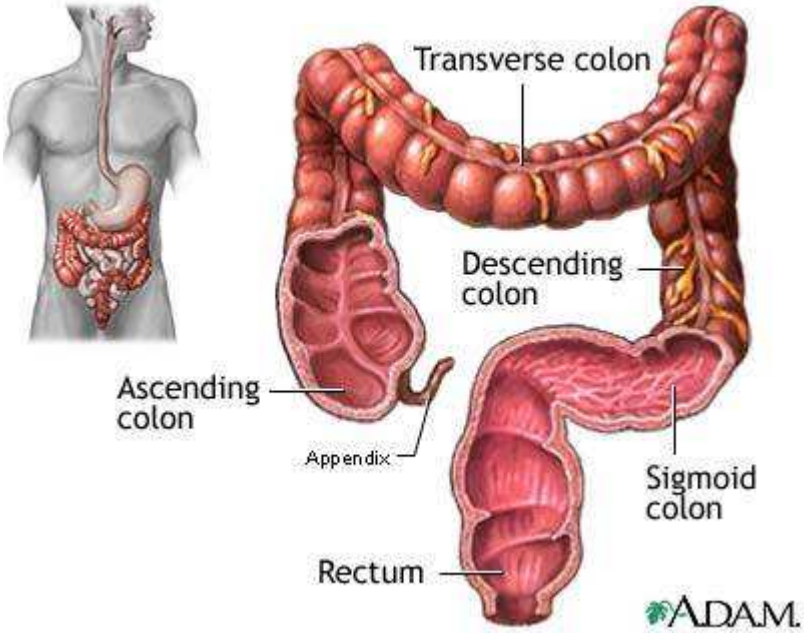
Roles for DNA methylation

- **Silencing parasitic DNA elements such as transposons, retroviruses, etc**
- **Genomic imprinting – controlling maternal or paternal-specific gene expression**
- **X inactivation**
- **Tissue or cell-specific gene expression**

Aberrant epigenetic events implicated in chronic diseases

- **CVD – Ordovás and Smith (2010)**
- **Type 2 diabetes mellitus – Pirola et al (2010), Wren and Garner (2005)**
- **Alzheimer's and cognitive disorders – Chouliaras et al. (2010), Gräff and Mansuy (2009)**
- **Cancer….**

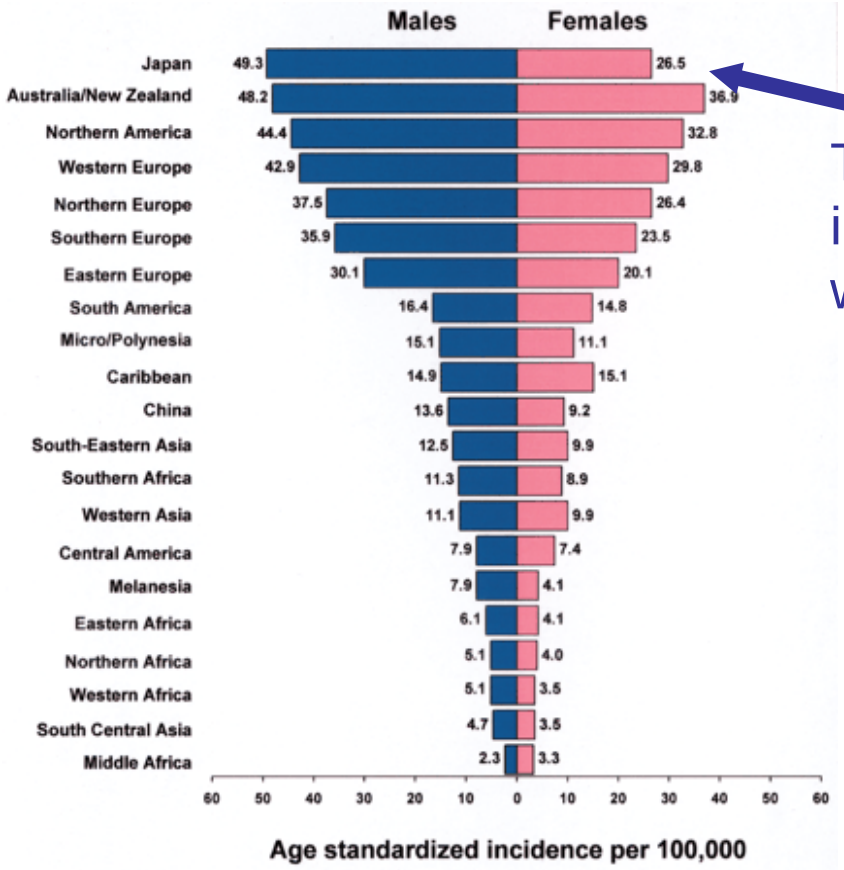
Colon (Bowel) Cancer



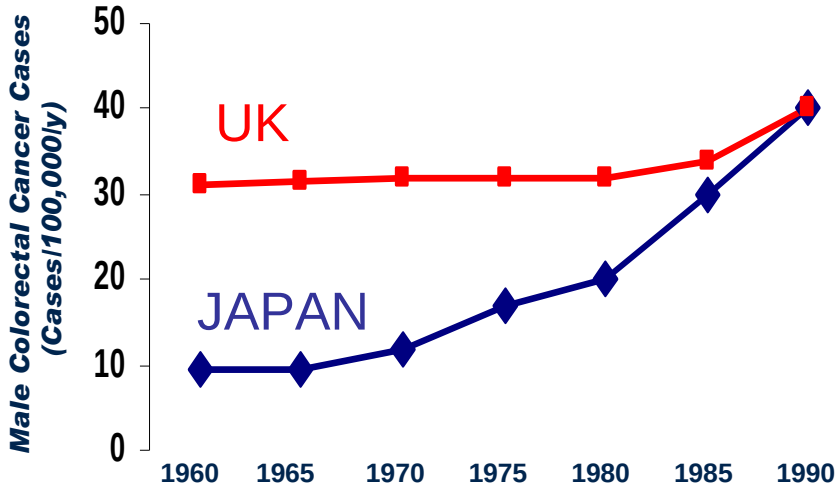
- 3rd most common cancer in UK (>37,500 new cases / year)
- Men > women (~2:1)
- ~16,000 deaths / year (16% down in last decade)
- ~50% of newly diagnosed will survive >5 years (doubled in last 30 years)

The role of lifestyle in the risk of colon cancer.

Age-standardised incidence of CRC in 21 regions in 2002



The increasing Incidence of colorectal cancer in Japan during the 20th century coincided with westernisation of the diet/lifestyle.

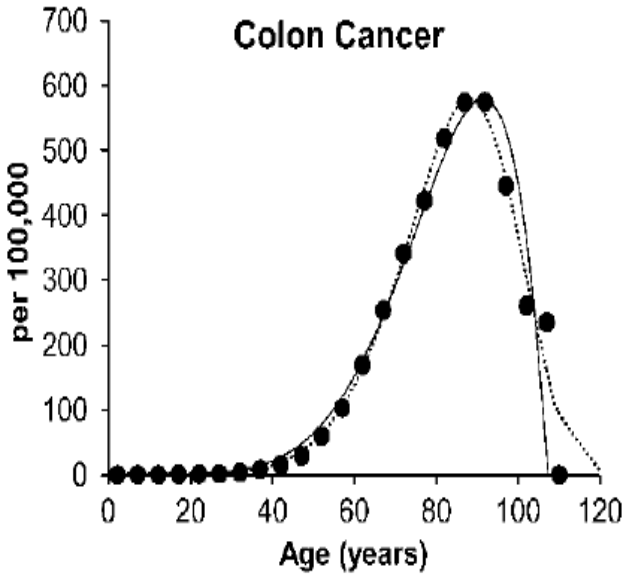


Parkin et al (2005) "Global Cancer Statistics 2002", CA Cancer J Clin 55, 74-108

From Key et al (2002) Lancet 861-868

Cancer and Ageing

- Age is the number one risk factor for colon cancer



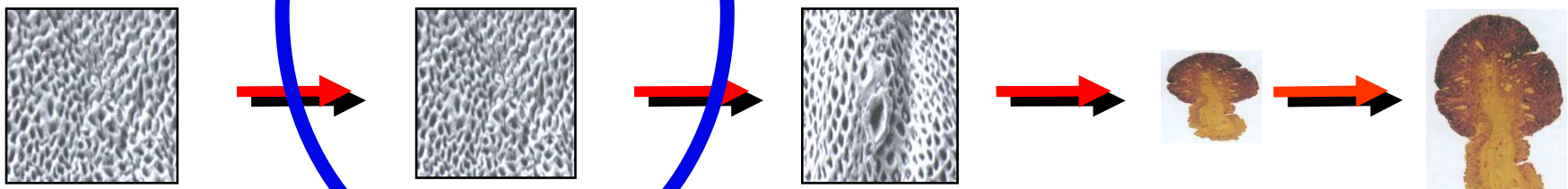
Harding et al (2008) Cancer Res.

- Age has even been called a potent carcinogen (DePinho (2000) Nature)

- Age-associated changes in the colon include more cell proliferation and less cell death

The adenoma-carcinoma sequence is the general model for colorectal carcinogenesis…

1	2	3	4	5
"Normal" Mucosa	*"Vulnerable" mucosa*	*Aberrant Crypts*	*Small Adenoma*	*Carcinoma*



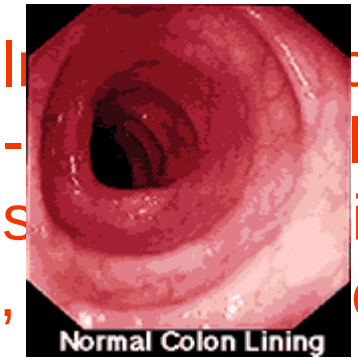
Genetic changes (somatic mutations e.g. APC, K-ras)

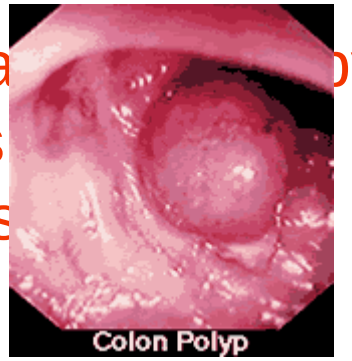
Epigenetic changes (aberrant DNA methylation)

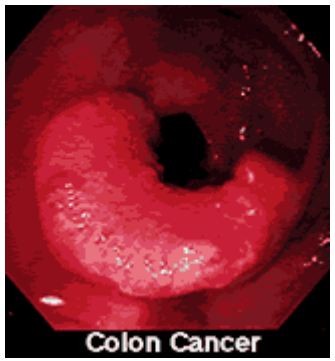
Precancerous Field Changes

Disease Process

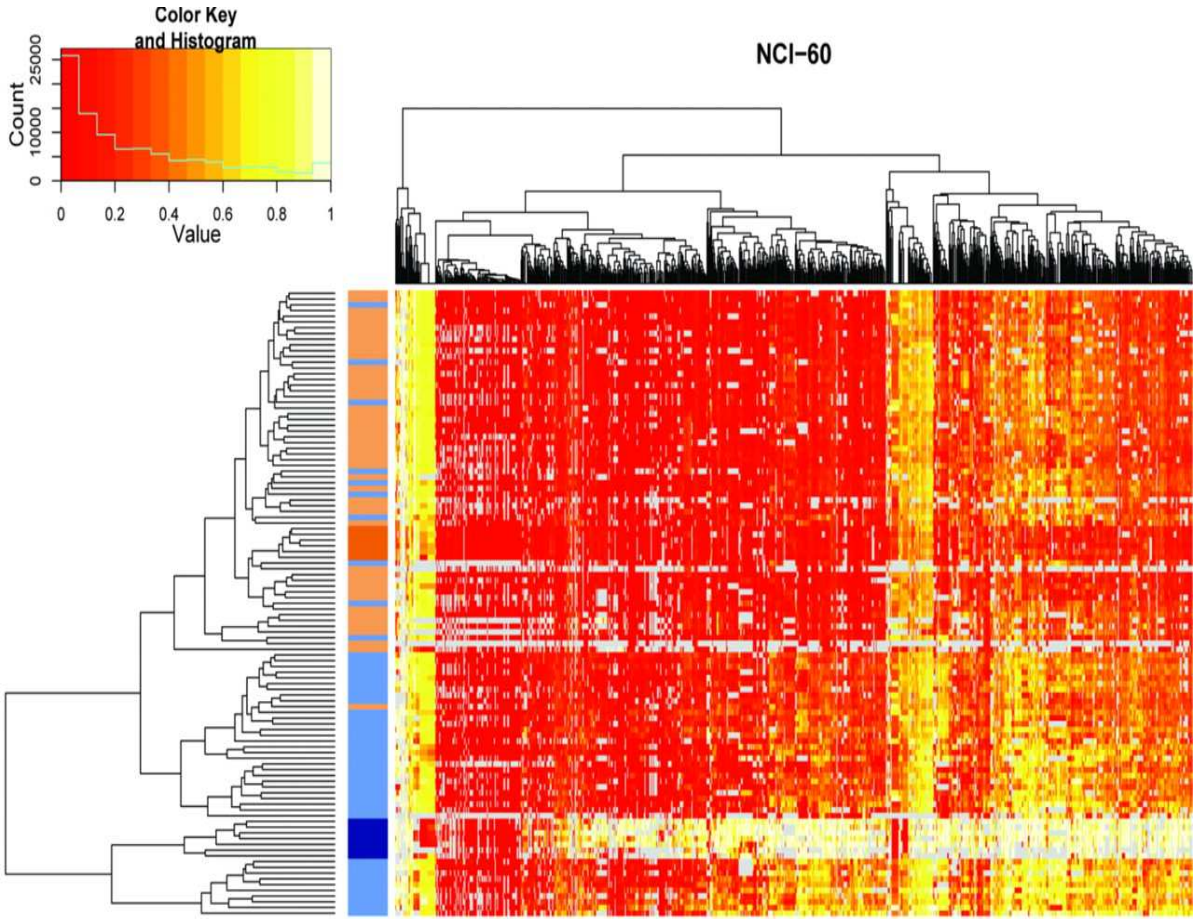
The vul cosa is cha by
an age- loss of tiss
homeos ing increas
growth, cell death,







Abnormal DNA methylation in colon cancer



- 7 colon cancer cell lines
- 48 colon cancer samples
- 48 normal tissue samples
- 6 normal control DNAs

~3 different groups of tumours.
Different prognoses?
Different treaments?

Ehrich M et al. PNAS 2008;105:4844-4849

An early role for aberrant DNA methylation in colon carcinogenesis

Dnmt3b promotes tumorigenesis in vivo by gene-specific de novo methylation and transcriptional silencing

Heinz G. Linhart,[1] Haijiang Lin,[1,6] Yasuhiro Yamada,[2] Eva Moran,[1] Eveline J. Steine,[1] Sumita Gokhale,[1] Grace Lo,[3] Erika Cantu,[3] Mathias Ehrich,[4] Timothy He,[5] Alex Meissner,[1] and Rudolf Jaenisch[1,3,7]

Genes and Development (2007) 21, 3110-22

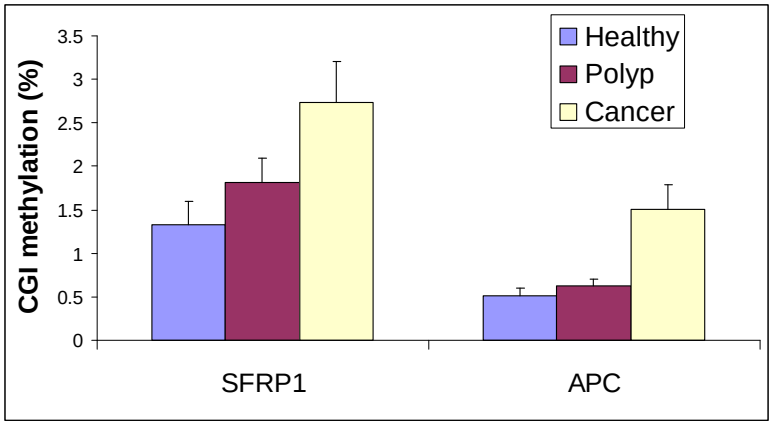
Genes methylated by DNA methyltransferase 3b are similar in mouse intestine and human colon cancer

Eveline J. Steine,[1] Mathias Ehrich,[2] George W. Bell,[1] Arjun Raj,[3] Seshamma Reddy,[1] Alexander van Oudenaarden,[3] Rudolf Jaenisch,[1] and Heinz G. Linhart[1,4,5]

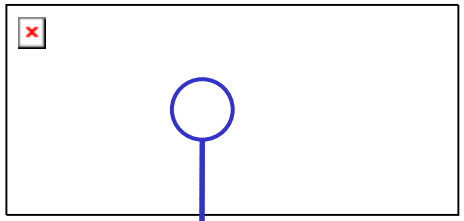
J. Clin. Invest. (2011) 121, 1748-52

Aberrant DNA methylation is associated with the field effect…

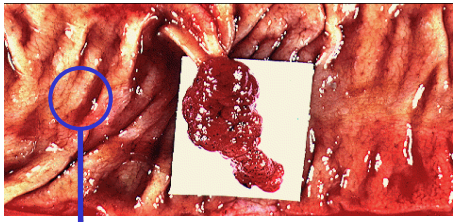
CGI methylation profiling in the **morphologically normal** mucosa



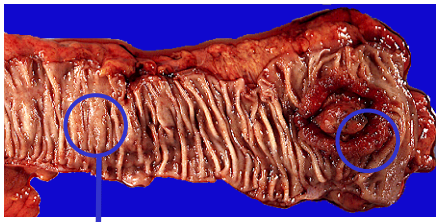
patients free of polyps or cancer



polyp patients



cancer patients

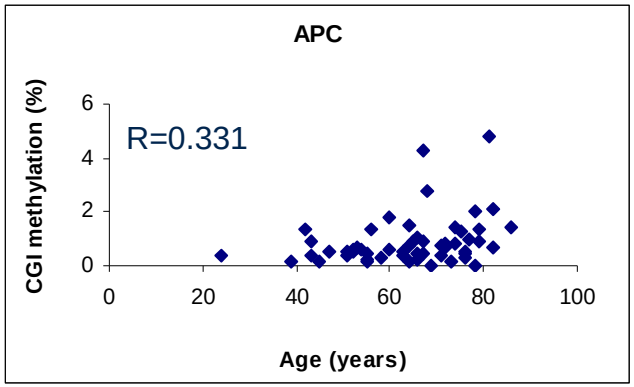


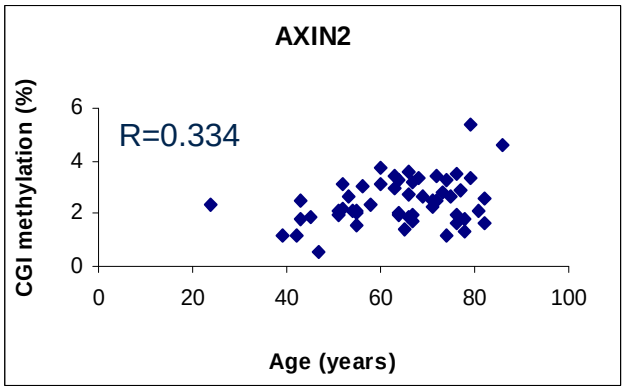
Sensitivity=62%, Specificity=79% (p=0.0167)
SFRP5, WIF1 and SFRP4

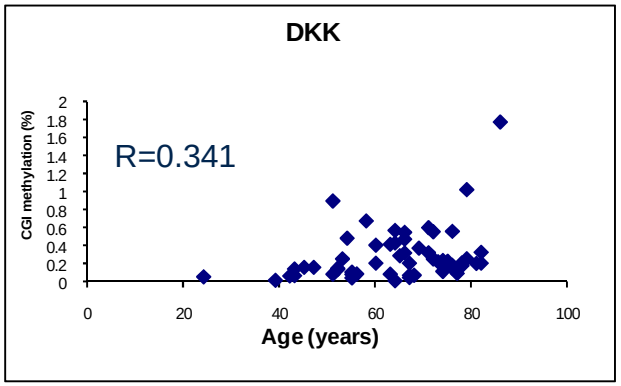
Sensitivity=84%, Specificity=70% (p=1.25x10^{-5})
APC, HPP1, p16, SFRP4, ESR1 and WIF1

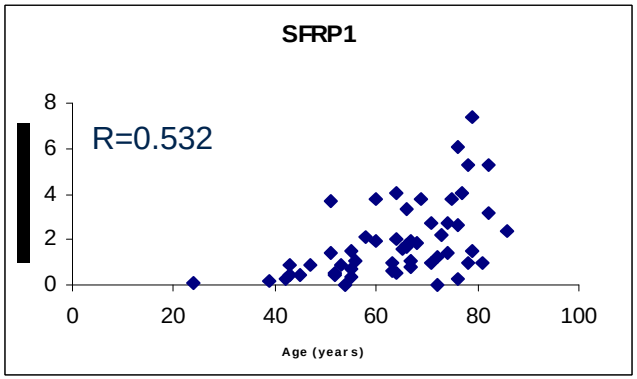
(Belshaw et al. 2008)

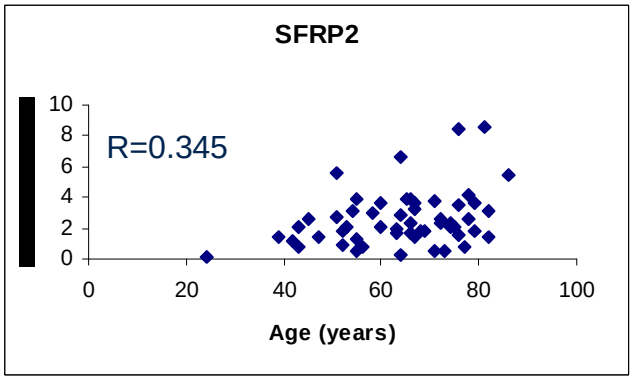
Many genes are aberrantly methylated in normal tissue in an age-dependent manner.....

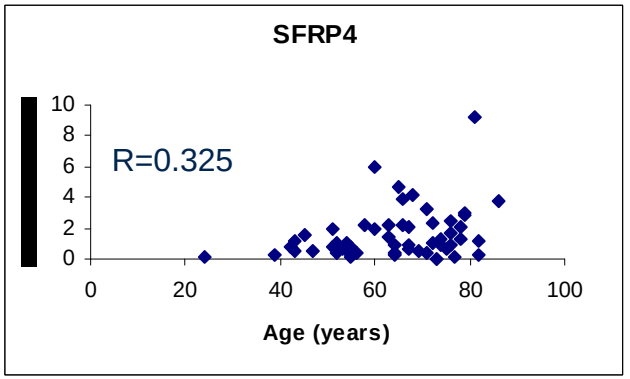












(Belshaw et al. 2008)

Epigenetic differences arise during the lifetime of monozygotic twins

Mario F. Fraga*, Esteban Ballestar*, María F. Paz*, Santiago Ropero*, Fernando Setien*, María 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*§§

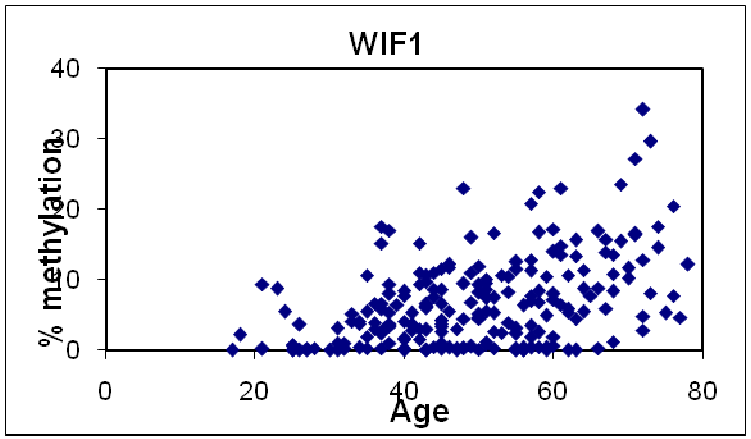
*Epigenetics, §Cytogenetics, and ¶Genetic Laboratories, Spanish National Cancer Centre (CNIO), Melchor Fernandez Almagro 3, 28029 Madrid, Spain; †Department of Behavioral Science, University of Valencia, 46010 Valencia, Spain; ‡Molecular Genetics Laboratory, Genetics Department, Son Dureta Hospital, 07014 Palma de Mallorca, Spain; ‖Department of Clinical Sciences, University Hospital Malmo, Lund University, S-205 02 Malmo, Sweden; **Steno Diabetes Center, 2820 Gentofte, Denmark; ††Twin Research and Genetic Epidemiology Unit, St. Thomas' Hospital, London SE1 7EH, United Kingdom; and ‡‡Human Cancer Genetics Program, Department of Molecular Virology, Immunology, and Medical Genetics, Ohio State University, Columbus, OH 43210

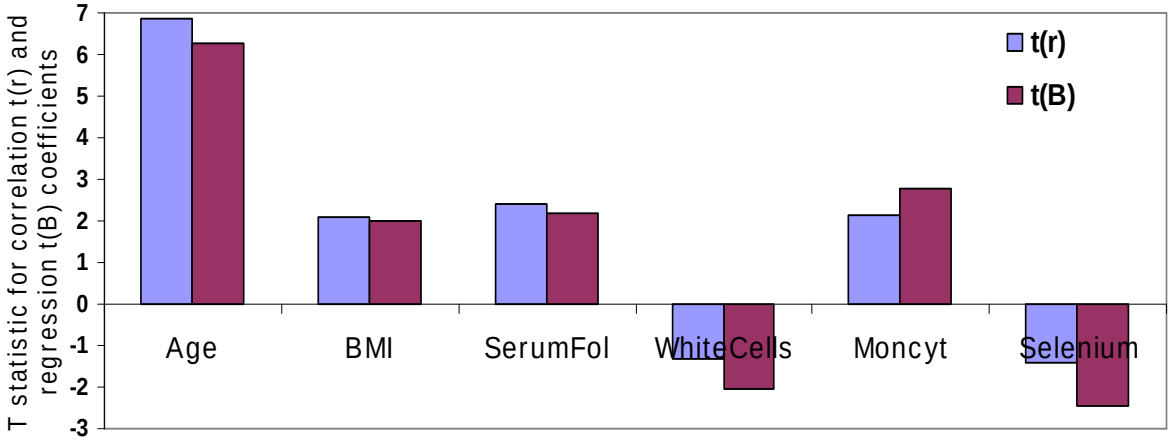
Edited by Stanley M. Gartler, University of Washington, Seattle, WA, and approved May 23, 2005 (received for review January 17, 2005)

- Young MZ twins are epigenetically very similar but diverge with age.
- Divergence is greatest in twins who have spent the longest time apart suggesting epigenetic drift (age-related methylation) is due to lifestyle.
- Cell types studied – lymphocytes, buccal, muscle and adipose

The impact of age, nutrition and metabolic factors on DNA methylation in the colonic mucosa

- **Cross-sectional study of >200 healthy volunteers with significant meta-data**
- **Quantified the methylation status of several genes in normal colon tissue**





Cofactor	*r*	p[1] (*r*)	B	p (B)
Age	0.447	1.004E-10	2.411	2.580E-09
BMI	0.150	0.039	0.760	0.046
SerumFolate	0.173	0.017	0.872	0.030
WhiteCells	-0.095	0.194	-0.902	0.044
Monocytes	0.155	0.032	1.218	0.006
Selenium	-0.103	0.155	-0.963	0.016

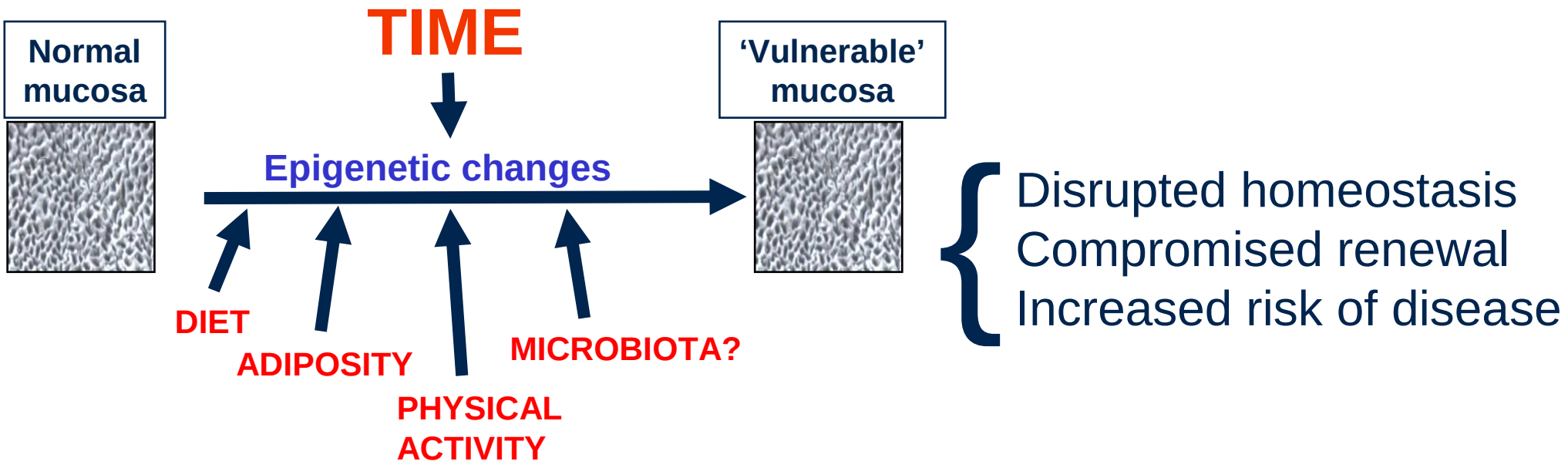
Variables contributing significantly to the variation in DNA methylation selected by genetic algorithm

WIF1	Age	BMI	Serum Folate	White Cells	Monocytes	Selenium
SFRP1	Age	Red Cell Folate	Monocytes			
SFRP2	Age	Fatness Index				
APC	Age	Vitamin D	Fatness Index			
SOX17	Age	White Cells				
HPP1	Age	Monocytes				
ESR1	Age	Height				
MYOD	Age	Serum Folate	Vitamin D			
N33	Age	Waist	Serum Folate			
PCA1	Age	Serum Folate	Vitamin D	Selenium		

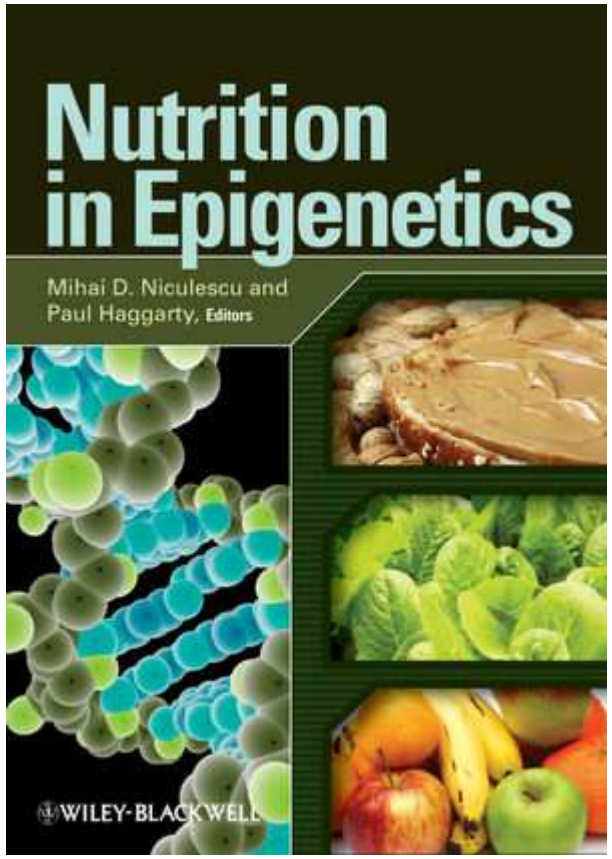
Positive correlation
Negative correlation

Sex-specific effect

The maintenance of gut health – preventing mucosal vulnerability



- Do these epigenetic changes compromise tissue homeostasis?
- How is the "environmental signal" transduced to the epigenome?
- Are these epigenetic changes reversible?



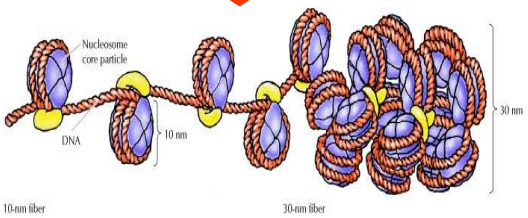
Nutrition in Epigenetics
Mihai D. Niculescu (Editor),
Paul Haggarty (Editor)
ISBN: 978-0-8138-1605-0
May 2011, Wiley-Blackwell

The importance of DNA methylation

- **It a flexible genomic parameter that can change in response to exogenous influences**
- **It constitutes a missing link between genetics, disease and the environment (perhaps especially diet)**
- **It is widely thought to play a significant (perhaps decisive) role in the aetiology of many human pathologies and ageing.**

Epigenetic changes: how the genome learns from experience

TIME



Epigenetic changes

Altered gene expression

Altered phenotype

DIET, LIFESTYLE
+ENVIRONMENT

Future prospects

- **Epigenetic epidemiology and Epigenome-wide association studies (EWAS)**
- **Novel (predictive) biomarkers of health/(risk of) disease**
- **Reversibility**

Strategic Relevance

BBSRC's strategic research priority 3 – Basic bioscience underpinning health

- "Basic bioscience is vital to reveal the biological mechanisms underlying normal physiology and homeostatic control during early development and through life."

- "A key research goal is to develop a better understanding of the role of diet and physical activity and the mechanisms by which they affect development and health."

Some key priorities 2010-2015

- Generate new knowledge of the biological mechanisms of ageing, and the maintenance of health

- **Establish greater understanding of how diet affects health throughout life, including EPIGENETIC effects, complex dietary exposures and gut function**

Acknowledgements

IFR

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UEA

Mark Williams and team

NNUH

Mike Lewis
Nandita Pal
Jamie Sington

Newcastle University

John Mathers and team

Washington University

Annette Fitzpatrick

BBSRC bioscience for the future

Food Standards Agency

National Institutes of Health

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