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Epigenetics, A Link between Environmental Pollutants and Cancer?
- Can we do better to prevent cancer?

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Cancer, A Worldwide Public Health Problem

Cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012.

The most common causes of cancer death are cancers of:

- lung (1.59 million deaths)
- liver (745 000 deaths)
- stomach (723 000 deaths)
- **colorectal (694 000 deaths)**
- **breast (521 000 deaths)**
- oesophageal cancer (400 000 deaths)

The International Agency for Research on Cancer (IARC) 2014

What Causes Cancer?

Cancer is a result of the interaction between the genetic factors and environmental/lifestyle factors:

- Lifestyle factors: Diet, physical inactivity, alcohol, smoking
- **Chemical carcinogens, such as** asbestos, components of tobacco smoke, aflatoxin (a food contaminant); **toxic heavy metals, air pollutants, plastic- and fast-food related chemicals, and pesticides…**
- Biological carcinogens, such as infections from certain viruses, bacteria or parasites

Is Cancer Preventable?

More than 30% of cancer deaths could be prevented by

Modifying or avoiding key risk factors, including:

- Lifestyle improvement
- **Improve our environment/reduce environmental exposure**
- Treatment of infection

Early detection

- **Early diagnosis**
- **Screening:** HPV testing for cervical cancer;PAP cytology test for cervical cancer; mammography screening for breast cancer

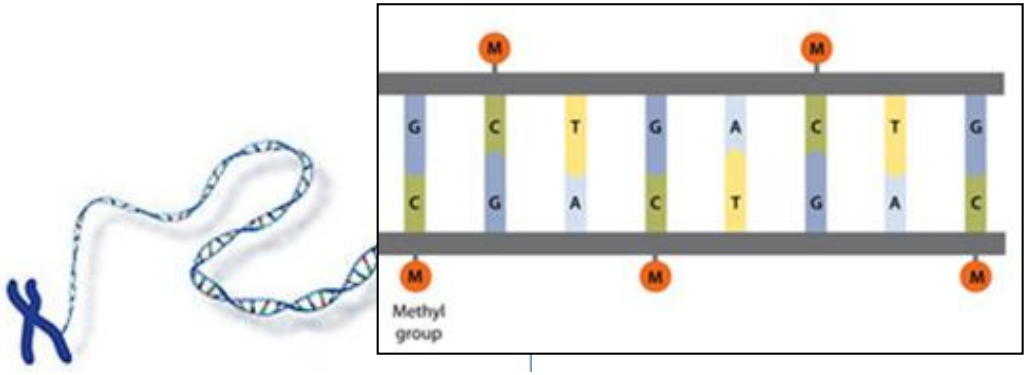
Intervention: Chemical agents, behavioral intervention

Modifying or avoiding key risk factors

Epigenetics?

- Study of mechanisms that regulate gene expression states without changes in DNA sequence
  - Genetically determined
  - **Environmentally Inducible**
  - **Reversible**

Epigenetics?



- Epigenetics is the interface between the fixed genetics and ever-changing environment

Three Epigenetic Components

- **Histone modifications**:
  - Globular proteins that undergo posttranslational modifications
  - Histone acetylation increases gene expression activity
  - Histone methylation inhibit or increase gene expression depending on the modified amino acid position

- **MicroRNAs (microRNAs):**
  - A set of small and non-protein-coding RNAs.
  - microRNAs regulate expression of target genes at the posttranscriptional level by binding to 3'-untranslated regions of target mRNAs

- **DNA methylation**:
  - Occurs at CpG sites
  - Addition of a methyl group to the 5′ position of the cytosine ring
  - Gene-specific methylation changes and global hypomethylation

DNA Methylation Modifiers

- Aging
- Diet/Nutrition
- Lifestyle factors
- Inflammation
- Environmental pollutants

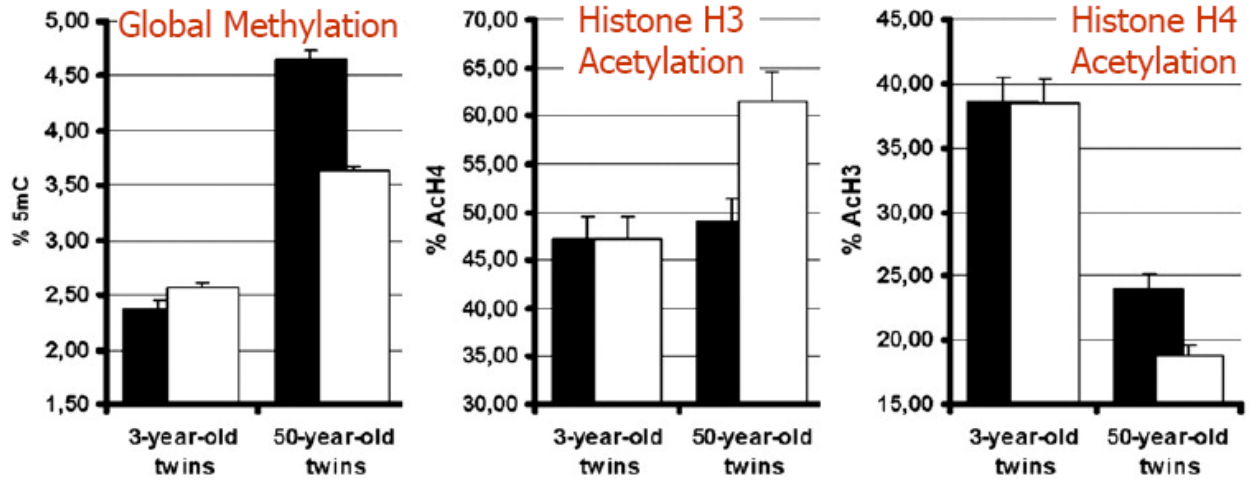
Epigenetic Markers - Genetically Determined and Environmentally Regulated

Twin Epigenetics

Epigenetic Markers - Genetically Determined and Environmentally Regulated

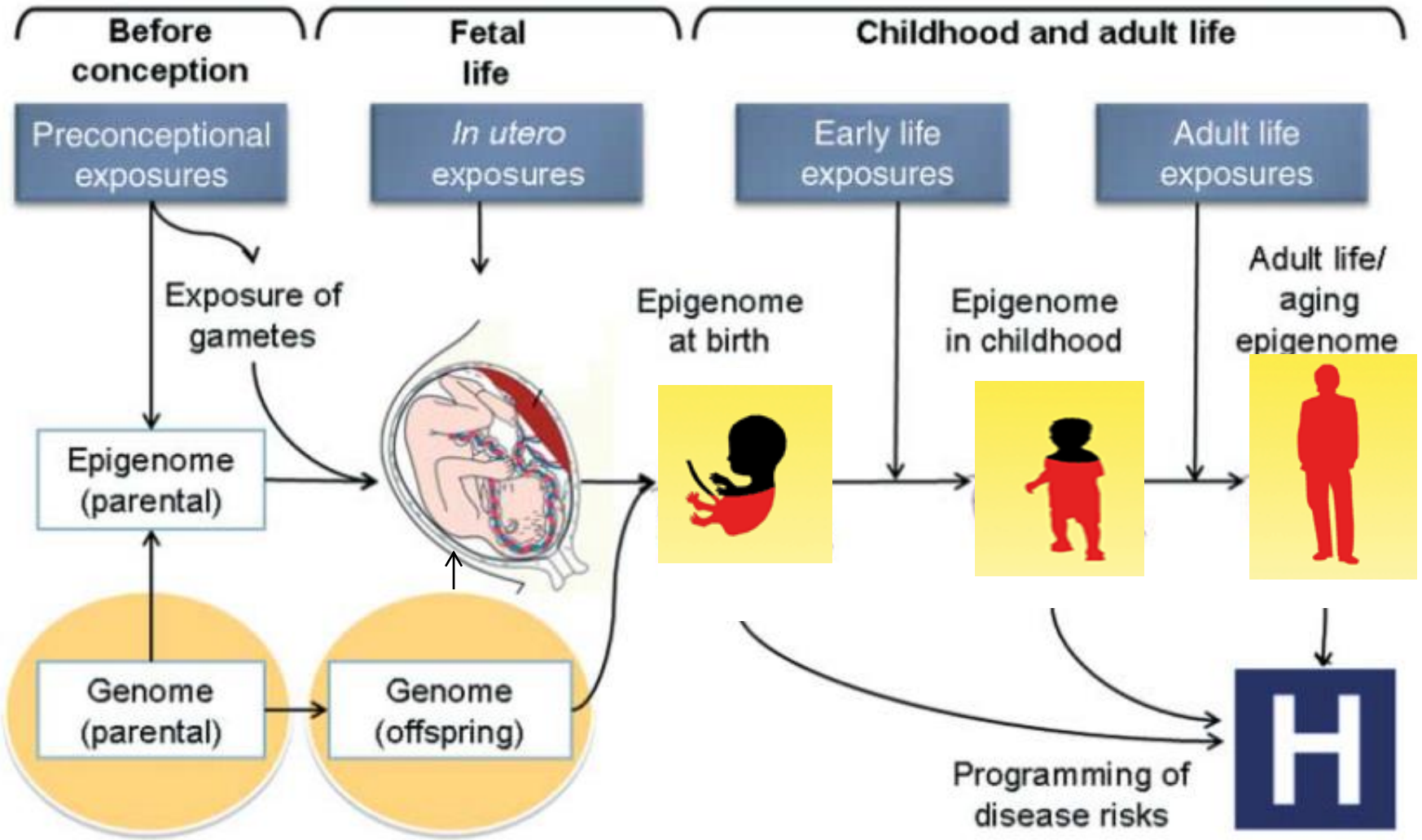
Twin epigenetics

Analysis of 80 MZ Twin Pairs between 3-73 years of age



(Braga et al. PNAS 2005)

A Life Course Perspective of Epigenetics



Fleisch et al. Journal of Molecular Endocrinology (2012) 49, R61–R67

Environmental Pollutants may Cause Cancer via Epigenetic Mechanism

Burden of Cancer in China

- In China, 3.1 million patients were diagnosed with cancer and 2.2 million deaths caused by cancer in 2012.(WHO, 2014)

- In 2012, more than half of global new cases of liver cancer and esophageal cancer were in China, as well as 51% and 49% mortality cases, respectively. 40% of global incidence and mortality of stomach cancer cases were in China as well as one third of global lung cancer cases. (WHO, 2014)

Environmental Pollution - A Major Public Health Concern

Air Pollution

- Seven cities in China are ranked among the ten most polluted cities in the world.(Asian Development Bank, 2012)

- Less than 1% of the 500 largest cities in China meet the air quality standards recommended by WHO (PM_{10}<20 μg/m^3).(Asian Development Bank, 2012)

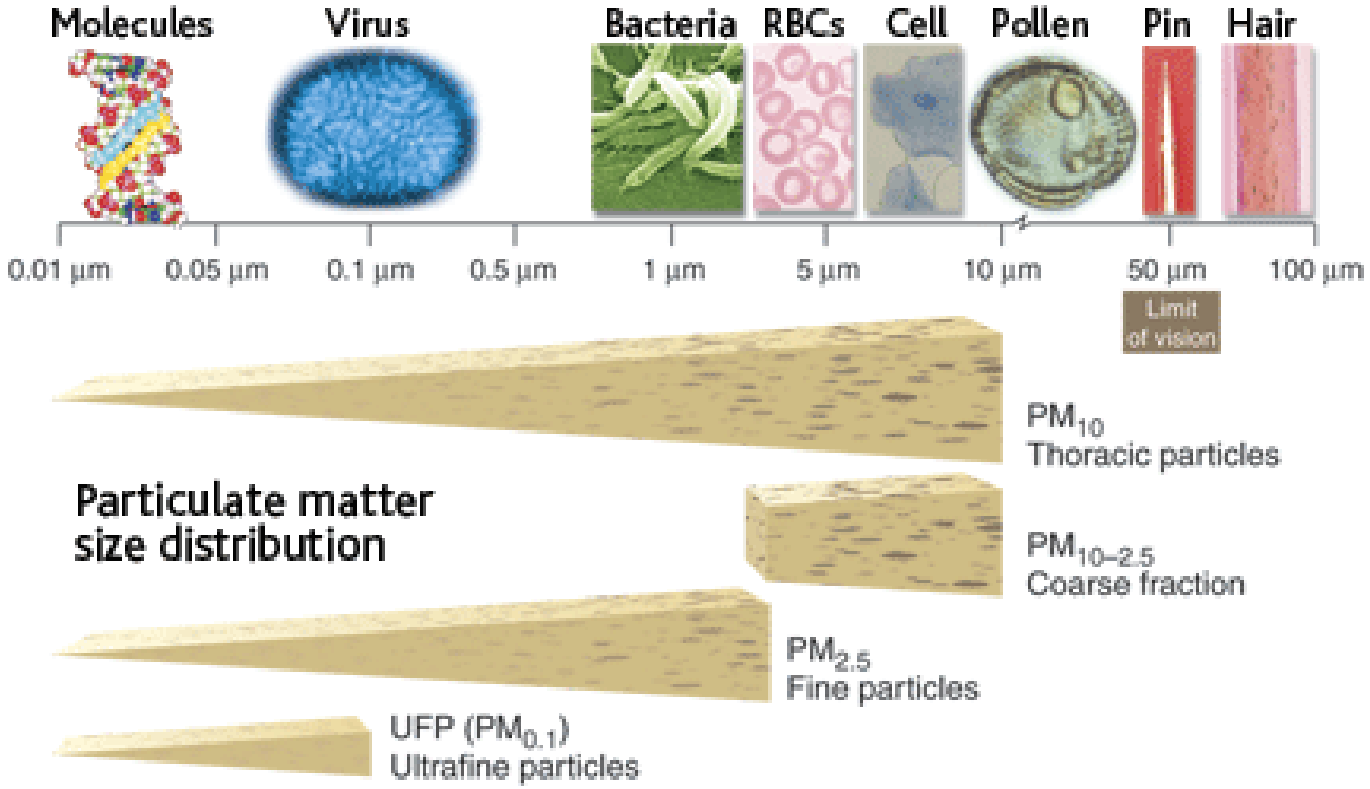
- According to 2010 Global Burden of Disease (GBD) report, each year 1.2 million deaths and 25 million health life year lost are due to air pollution in China. (WHO, 2012)

Air Pollution in Beijing (2014.10.08)

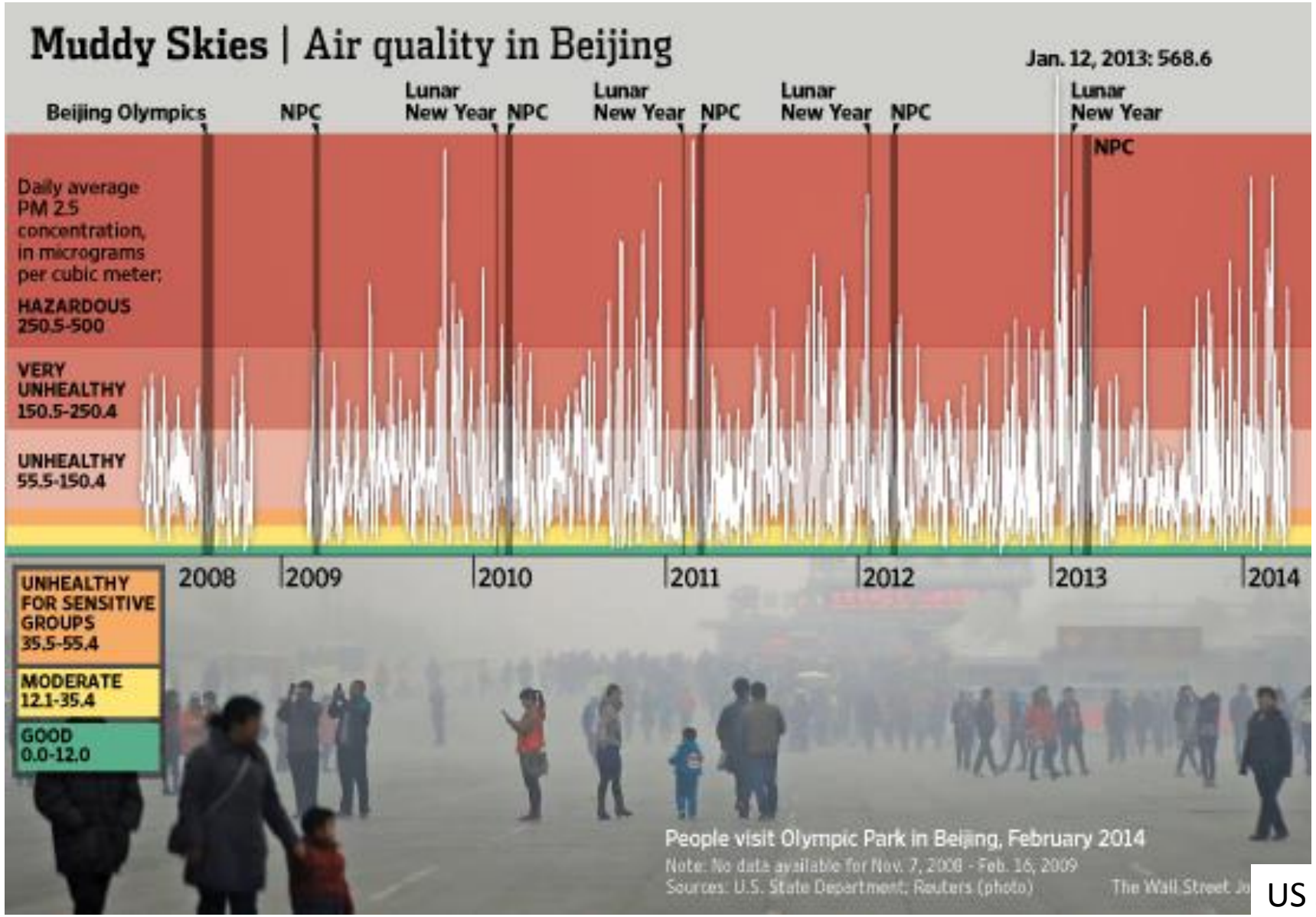
Air pollutants

Air pollution: causing approximately 800,000 deaths worldwide on annual basis

Particulate Matter (PM) - Complex mixture of solid and liquid particles - combustion products, sulphates, nitrates, metals, biological materials



Daily $PM_{2.5}$ Level in Beijing between 2008-2014



US State Department, 2014

Air Pollution in Beijing

- Traffic derived air pollution is particularly critical in Beijing
  - Very high population density
  - Rapid increase in vehicles
  - Limited control of emissions
  - Factories in and around Beijing

- Providing a unique research opportunity for identifying potential PM-induced molecular changes that may not easily be detectable in low exposed populations

Our Beijing Air Pollution Study, 2008

- **Particle Mass:** $PM_{2.5}$ measured using active portable samplers
- **Traffic Particles:** Elemental Carbon (EC) measured by reflectance on $PM_{2.5}$ filters

Group	$PM_{2.5}$ ($\mu g/m^3$)		EC ($\mu g/m^3$)	
	Mean (SD)	P value	Mean (SD)	P value
Office workers (n=120)	94.6 (64.9)	Ref.	13.1 (4.0)	Ref.
Truck Drivers (n=120)	126.8 (68.8)	<0.001	17.3 (6.7)	<0.001

Beijing Air Pollution Study

Results

- Mitochondrial MT-TF and MT-RNR1 DNA methylation was positively associated with metal-rich PM exposure.

- Decreased blood and mtDNA copy number with increased exposure to black carbon and ambient PM_{10} exposure.

Byun *et al. Particle and Fibre Toxicology* 2013, **10**:18
http://www.particleandfibretoxicology.com/content/10/1/18

RESEARCH Open Access

Effects of airborne pollutants on mitochondrial DNA Methylation

Hyang-Min Byun[1,6*], Tommaso Panni[1,2], Valeria Motta[1,3], Lifang Hou[4], Francesco Nordio[1], Pietro Apostoli[5], Pier Alberto Bertazzi[3] and Andrea A Baccarelli[1]

Inhalable particulate matter and mitochondrial DNA copy number in highly exposed individuals in Beijing, China: a repeated-measure study

Lifang Hou[1,2*†], Xiao Zhang[1†], Laura Dioni[3,4], Francesco Barretta[3,4], Chang Dou[5], Yinan Zheng[1], Mirjam Hoxha[3,4], Pier Alberto Bertazzi[3,4], Joel Schwartz[6], Shanshan Wu[7], Sheng Wang[8*] and Andrea A Baccarelli[6]

Beijing Air Pollution Study

Results

- Exposure to PM and its heavy metals is associated with hypo-methylation tandem repeats that were found to associated with cancers.
- Measuring tandem-repeat hypo-methylation in easy-to-obtain blood specimens might identify individuals with biological effects and potential cancer risk from PM exposure.

Environmental and Molecular Mutagenesis
Environmental Mutagenesis and Genomics Society

Altered Methylation in Tandem Repeat Element and Elemental Component Levels in Inhalable Air Particles

Lifang Hou,[1,2*] Xiao Zhang,[1] Yinan Zheng,[3] Sheng Wang,[4*] Chang Dou,[5] Liqiong Guo,[6,7] Hyang-Min Byun,[6] Valeria Motta,[6] John McCracken,[6] Anaité Díaz,[8] Choong-Min Kang,[6] Petros Koutrakis,[6] Pier Alberto Bertazzi,[9] Jingyun Li,[10] Joel Schwartz,[6] and Andrea A. Baccarelli[6]

Effects of short-term exposure to inhalable particulate matter on DNA methylation of tandem repeats

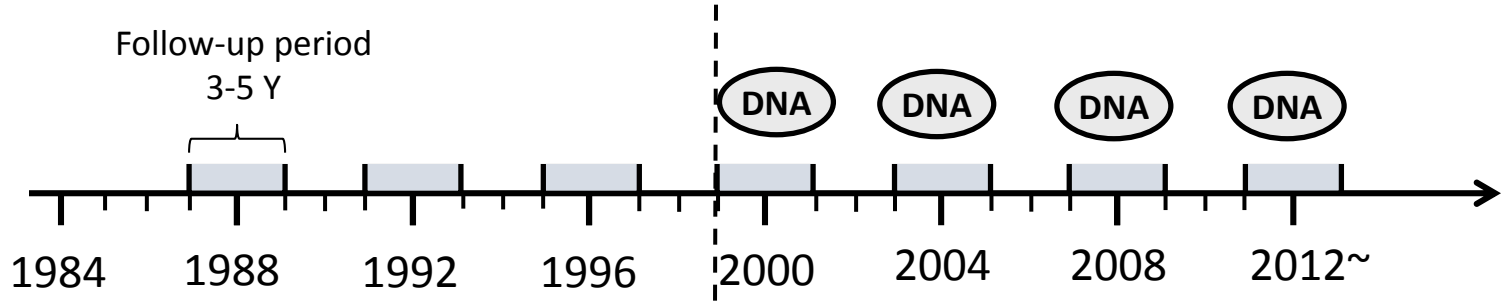
Liqiong Guo[1,2,†,*], Hyang-Min Byun[1], Jia Zhong[1], Valeria Motta[1,3], Jitendra Barupal[1], Yinan Zheng[4], Chang Dou[5], Feiruo Zhang[6], John P. McCracken[1], Anaité Diaz[7], Sanchez-Guerra Marco[1], Silvia Colicino[3], Joel Schwartz[1], Sheng Wang[6], Lifang Hou[8,9] andAndrea A. Baccarelli[1,†]

DNA Methylation and Cancer Incidence and Mortality in a US Population

Normative Aging Study (NAS) Cohort

- **NAS cohort (1963 ~ Now):**
  - N=2280
  - Age at enrollment: 20–70 years old
  - Longitudinal investigation of aging in Boston Area

- **Follow-Up:**
  - Questionnaire and medical examinations every 3 to 5 years;
  - Blood donation and genetic/epigenetic biomarkers were available since **1999**.



Cancer Incidence and Mortality Follow-up

- **Baseline Cancer**
  - Study subjects with cancer: 219 (28% of 794)
  - Cancer free: 575 (72% of 794)
- **Incidence Follow-up** (n=575)
  - Median incidence follow-up time: 114 months (6,222 person-year)
  - Cancer diagnoses were confirmed on clinical records
  - Results: **130 new cases**
- **Mortality Follow-up** (n=793, 1 participant had unknown date of death)
  - Median mortality follow-up time : 172 months (9,449 person-year)
  - Questionnaires and death certificate
  - Results: **67 deaths from cancer**

Methylation Markers Studied

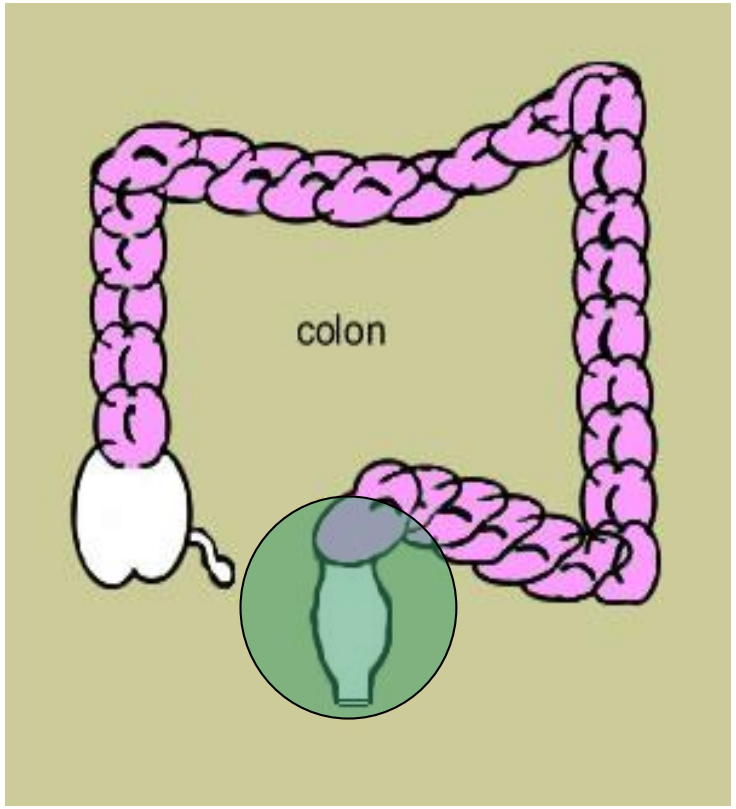
- Alu
- LINE-1
- Intercellular adhesion molecule-1 (ICAM)
- Interferon gamma (IFNɣ)
- Interleukin-6 (IL6)
- Toll-like receptor-2 (TLR2)
- Inducible nitric oxide synthase (iNOS)
- 8-oxoguanine DNA glycosylase (OGG)
- Carnitine acetyltransferase (CRAT)
- **Genome wide DNA methylation**

Application of Optical Biomarkers to Early Detection of Gastrointestinal (GI) Cancers

Field Carcinogenesis and Cancer Early Detection

- **Ideal markers for early cancer detection:**
  Simple, minimally intrusive, sufficiently sensitive, and cost-effective

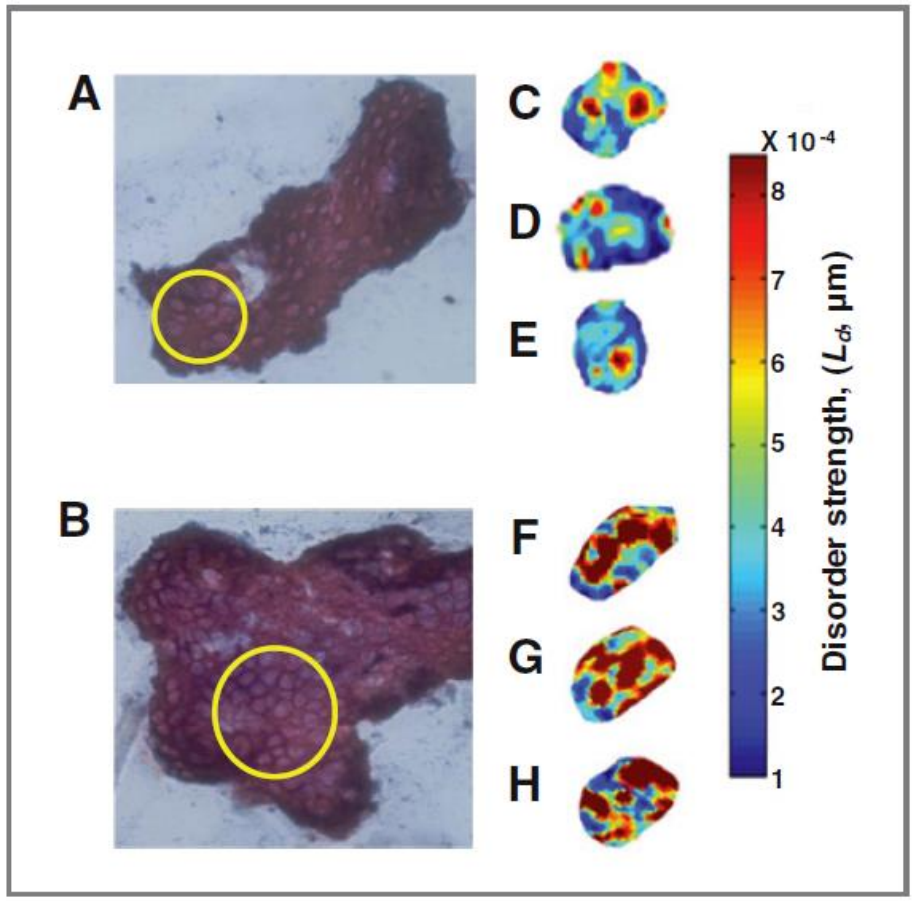
- **Field Carcinogenesis**
  - Increased susceptibility of an entire area to carcinogenesis
  - It represents the impact of the field-of-injury concept that the genetic and environmental risk factors confer a fertile mutational field throughout the area



Field Carcinogenesis Detection Using PWS

- Partial-Wave Spectroscopy (PWS) enables the sensitive detection of nanoscale cellular structural changes in field carcinogenesis
- Cellular Nano-architectural changes precede the microscopic morphological changes
- Visible-light microscopy allows morphological analysis only at micron scales due to the diffraction limit
- **Number of cells: 30**
- PWS analysis is performed off-site

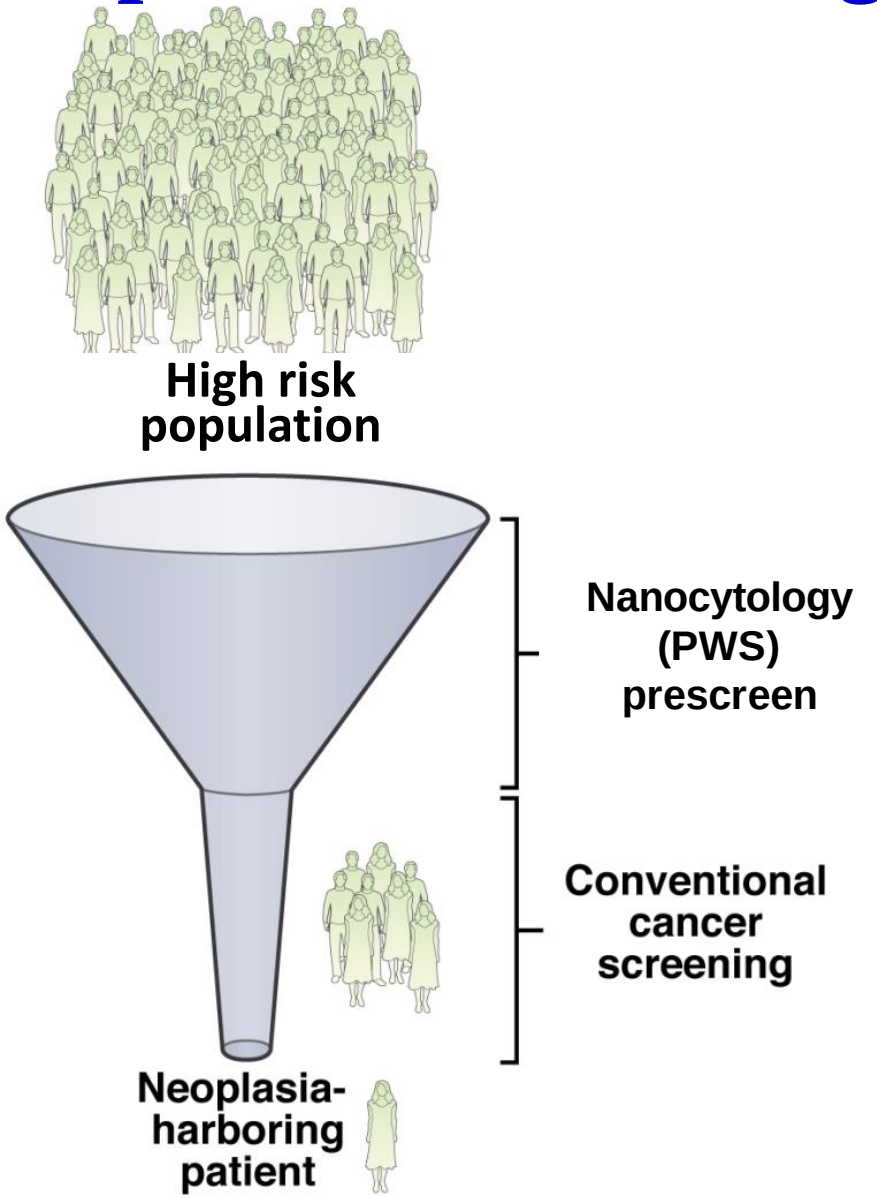
PWS Image of Rectal Colonocytes from Control and Colon Cancer Patients



Representative PWS generated pseudocolor heatmap of Ld for the colonocytes from the circled region of control patient (C–E) and similarly are for patients with cancer (F–H).

Cancer Res; 72(11) June 1, 2012, Damania, Roy, and Backman

Clinical Implications-Approach to Population Screening



Validation of optical biomarkers In large population - Shanghai PWS and Gastrointestinal Track Cancer Study

Why China?

- Fast patient recruitment
- Low cost
- Large patients' pool
- Cancers different from US

  - Different risk factors (Liver cancer)
  - Different incident/mortality rate (prostate, gastric)

Take Home Message:

- Environmental pollutants may cause cancers via epigenetic mechanism
- Educate the general population to live a healthy lifestyle
- Early detection is the key for cancer prevention
- Invention may be a solution to prevent highly-exposed individuals from cancer development – long way to go!
- Large population-based researches are urgently needed in different populations

Thank You!

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