MECHANISTIC APPROACHES TO THE PREVENTION OF MUTATION AND CANCER

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University of Genoa, Italy

Department of Health Sciences
Section of Hygiene and Preventive Medicine
THE HIPPOCRATIC OATH

I swear by Apollo the Physician and Asclepius and Hygeia and Panaceia and all the gods and goddesses, making them my witnesses, that I will fulfill according to my ability and judgment this oath……
THE EPIDEMIOLOGICAL REVOLUTION OF THE 20th CENTURY
S. De Flora, A. Quaglia, C. Bennicelli & M. Vercelli, FASEB J. 19, 892–897, 2005

ITALY, 1901–2000 (RAW MORTALITY DATA)
THE EPIDEMIOLOGICAL REVOLUTION OF THE 20th CENTURY

S. De Flora, A. Quaglia, C. Bennicelli & M. Vercelli, FASEB J. 19, 892–897, 2005

ITALY, AGE-STANDARDIZED MORTALITY DATA

CEREBROVASCULAR DISEASES
M – 72.4%
F – 74.4%

CARDIOVASCULAR DISEASES
M – 51.9%
F – 67.9%

TUMORS
M – 18.3%
F – 12.9%

Deaths per 100,000

Primary Prevention

Inhibition of mutation and cancer initiation in the extracellular environment or in nontarget cells
1. Inhibition of uptake of mutagens/carcinogens
   1.1. Inhibition of penetration
   1.1.1. Inhibition of nitrosation reaction
   1.1.2. Modification of the intestinal microbial flora
   1.1.3. By physical or mechanical means
   1.1.4. By chemical reaction
   1.1.5. By enzyme–catalyzed reaction

Inhibition of mutation and cancer initiation in target cells
2. Modification of transmembrane transport
   2.1. Inhibition of cellular uptake
   2.1.1. Inhibition of oxidative phosphorylation
   2.1.2. Stimulation of extrusion outside cells

Inhibition of the endogenous formation of mutagens and carcinogens
3.1. Inhibition of the nitrosation reaction
3.2. Modification of the intestinal microbial flora
3.3. By physical or mechanical means
3.4. By chemical reaction
3.5. By enzyme–catalyzed reaction

Complexation, dilution, and/or deactivation of mutagens/carcinogens outside cells
4.1. By physical or mechanical means
4.2. By chemical reaction
4.3. By enzyme–catalyzed reaction

Protection of DNA nucleophilic sites
5.1. By physical or mechanical means
5.2. By chemical reaction
5.3. By enzyme–catalyzed reaction

Protection of intercellular communications
6.1. By physical or mechanical means
6.2. By chemical reaction
6.3. By enzyme–catalyzed reaction

Secondary Prevention

Inhibition of tumor promotion
3.1. Inhibition of genotoxic effects (see 1 and 2)
3.2. Antioxidant activity and scavenging of free radicals
3.3. Anti-inflammation activity
3.3.1. Cyclooxygenase inhibition
3.3.2. Lipooxygenase inhibition
3.3.3. Inhibition of inducible nitric oxide synthase
3.3.4. Leukotriene receptor antagonism
3.4. Inhibition of proteases
3.5. Inhibition of cell proliferation
3.5.1. Inhibition of ornithine decarboxylase
3.5.2. Promoting proteasomal degradation of cyclins
3.5.3. Interference with multiple signaling pathways
3.6. Induction of cell differentiation
3.7. Modulation of cell apoptosis
3.8. Signal transduction modulation
3.9. Protection of intercellular communications

Tertiary Prevention

Inhibition of invasion and metastasis
5.1. Antioxidant activity and scavenging of free radicals
5.2. Signal transduction modulation
5.3. Inhibition of cell proliferation (see 3.4)
5.4. Modulation of cell apoptosis
5.5. Induction of cell differentiation
5.6. Inhibition of angiogenesis
5.7. Effect on cell-adhesion molecules
5.8. Inhibition of proteases involved in basement membrane degradation and modulation of the interaction with the extracellular matrix
5.9. Activation of antimetastasis genes
1. Inhibition of mutation and cancer initiation in the extracellular environment or in nontarget cells

1.1. Inhibition of uptake of mutagens/carcinogens
   1.1.1. Inhibition of penetration
   1.1.2. Removal from the organism

1.2. Inhibition of the endogenous formation of mutagens and carcinogens
   1.2.1. Inhibition of the nitrosation reaction
   1.2.2. Modification of the intestinal microbial flora

1.3. Complexation, dilution and/or deactivation of mutagens/carcinogens outside cells
   1.3.1. By physical or mechanical means
   1.3.2. By chemical reaction
   1.3.3. By enzyme–catalyzed reaction

1.4. Favoring absorption of protective agents

1.5. Stimulation of trapping and detoxification in nontarget cells
2. Inhibition of mutation and cancer initiation in target cells

2.1. Modification of transmembrane transport
   2.1.1. Inhibition of cellular uptake
   2.1.2. Stimulation of extrusion outside cells

2.2. Modulation of metabolism
   2.2.1. Inhibition of activation of promutagens/procarcinogens by Phase I enzymes
   2.2.2. Induction of Phase I detoxification and Phase II conjugation pathways, or acceleration of decomposition of reactive metabolites
   2.2.3. Stimulation of activation, coordinated with detoxification and blocking of reactive metabolites

2.3. Blocking or competition
   2.3.1. Trapping of electrophiles by either chemical reaction or enzyme–catalyzed conjugation
   2.3.2. Antioxidant activity and scavenging of reactive species
   2.3.3. Protection of DNA nucleophilic sites

2.4. Inhibition of cell replication
2.5. Maintenance of DNA structure and modulation of DNA metabolism and repair
   2.5.1. Increase of fidelity of DNA replication and repair
   2.5.2. Stimulation of repair and/or reversion of DNA damage
   2.5.3. Inhibition of error-prone repair pathways
   2.5.4. Correction of hypomethylation
   2.5.5. Inhibition of histone deacetylation
   2.5.6. Blocking of telomerases or inhibition of their activity

2.6. Control of gene expression
   2.6.1. Targeted inactivation of oncogenes
   2.6.2. Inhibition of oncogene expression
   2.6.3. Inhibition of oncogene sequences or activity
      2.6.3.1. Inhibition of translation targeted to oncogene mRNA
      2.6.3.2. Inhibition of transcription of specific DNA sequences
      2.6.3.3. Blocking of target genes
      2.6.3.4. Farnesyltransferase inhibition
   2.6.4. Neutralization or post–translational modification of oncogene products
   2.6.5. Replacement of deleted tumor suppressor genes
   2.6.6. Mimicking the DNA binding of tumor suppressor genes by antiidiotypic antibodies
   2.6.7. Killing of cells lacking tumor suppressor genes
3. Inhibition of tumor promotion

3.1. Inhibition of genotoxic effects (see 1 and 2)
3.2. Antioxidant activity and scavenging of free radicals
3.3. Antiinflammatory activity
   3.3.1. Cyclooxygenase inhibition
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4. Inhibition of tumor progression
   4.1. Inhibition of genotoxic effects (see 1 and 2)
   4.2. Antioxidant activity and scavenging of free radicals
   4.3. Inhibition of proteases
   4.4. Signal transduction modulation
   4.5. Effects on the hormonal status
      4.5.1. Selective estrogen receptor modulation
      4.5.2. Aromatase inhibition
      4.5.3. Selective blocking of prostaglandin E₂ receptors
      4.5.4. Decrease in ovarian hormones by dietary isoflavones
      4.5.5. Inhibiting the pituitary secretion of luteinizing hormone
      4.5.6. Preventing conversion of testosterone into dehydrotestosterone by 5α-reductase
      4.5.7. Selective androgen receptor antagonism
   4.6. Effects on the immune system
   4.7. Inhibition of angiogenesis
   4.8. Antineoplastic activity by either mechanical, physical, chemical, or biological means
5. Inhibition of invasion and metastasis
   5.1. Antioxidant activity and scavenging of free radicals
   5.2. Signal transduction modulation
   5.3. Inhibition of cell proliferation (see 3.4)
   5.4. Modulation of cell apoptosis
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   5.9. Activation of antimetastasis genes
DECODING THE BLACK BOX

DEEPER UNDERSTANDING OF DISEASES AND RISK FACTORS

- Mutagenicity of escreta
- Analysis of metabolites
- Mutagenicity of escreta
- DNA adducts
- 8-oxo-dG
- Metabolic alterations
- DNA damage and repair
- Cytogenetic effects
- Activation of oncogenes
- Deletion/mutation of oncosuppressor genes
- Proliferation, differentiation, apoptosis, etc.

- Genes colored by: SHAM vs. CS, Default Interpretation (sham.txt)
- Gene List: mmu (484)

- Proteins
- mRNA
- tmRNA
- mRNAs

- Genes
- Proteins
- mRNAs
- tmRNAs

- MIRNOME
- TRANSRIPTOME
- PROTEOME
- DEEPER UNDERSTANDING OF DISEASES AND RISK FACTORS
**PROTECTIVE FACTORS**

- Broccoli
- Kiwi
- Tomatoes
- Yellow pepper

**RISK FACTORS**

- Smoking

**DISEASES**

**EXPOSURE MARKERS**

- Protein adducts
- DNA adducts
- 8-oxo-dG

**Analysis of metabolites**

**Mutagenicity of escreta**

**STOP**

**BIOLOGICALLY EFFECTIVE DOSE**

**Early biological damage**

**YEARS - DECADES**

**Metabolic alterations**

**DNA damage and repair**

**Cytogenetic effects**

**Activation of oncogenes**

**Deletion/mutation of oncosuppressor genes**

**Proliferation, differentiation, apoptosis, etc.**

**PROTEOME**

**GENOME**

**MIRNOME**

**TRANSCRIPTOME**

**SHAM vs CS, Default Interpretation**


**Nature Precedings**

**Risk Factors**

**Protective Factors**

**Early Biological Damage**

**Years - Decades**

**Biotransformation**

**Protein adducts**

**DNA adducts**

**8-oxo-dG**

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**Deletion/mutation of oncosuppressor genes**

**Proliferation, differentiation, apoptosis, etc.**

**PROTEOME**

**GENOME**

**MIRNOME**

**TRANSCRIPTOME**

**SHAM vs CS, Default Interpretation**

Pathological conditions

Cancer / Chemicals and complex mixtures
Pathological conditions

COPD

(A. Izzotti et al., FASEB J. 17, 1127-29, 2003)
(R. Balansky et al., Carcinogenesis 30, 1398-401, 2009)
Pathological conditions

Alopecia

(R. Balansky et al., PNAS USA 103, 7823-78, 2006)
Pathological conditions

Atherosclerosis
Pathological conditions

Heart diseases
Pathological conditions

Neurodegenerative diseases

(S. La Maestra et al., 2010)
Pathological conditions

Eye diseases

Pathological conditions

Rare genetic diseases

(A. Izzotti et al., Neurology 71, 610-2, 2008)
Physiological situations

Pregnancy

(A. Izzotti et al., FASEB J. 17, 1127-9, 2003)
Physiological situations

Perinatal period

Physiological situations

Aging

(R. Balansky et al., Cancer Res. 56, 1642-7, 1996)
Physiological situations

Stem cells

(S. De Flora et al., Int. J. Oncol. 29, 521-529, 2006)
GENOMIC CHANGES IN MOUSE LUNG AT BIRTH


Newborn mice / fetuses

<table>
<thead>
<tr>
<th>8-oxo-dGua</th>
<th>DNA adducts</th>
<th>Expression of 746 genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>P &lt; 0.05</td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

| 0.9        | 2.0         |
| NS         | NS          |

UNTREATED PREGNANT MICE

NAC–TREATED PREGNANT MICE
MICE EXPOSED TO SMOKE AFTER BIRTH

UNTREATED PREGNANT MICE

LUNG TUMORS: 61.1%
LUNG EMPHYSEMA: 16.7%
HYPERPLASIA OF BLADDER EPITHELIUM: 20.4%

NAC–TREATED PREGNANT MICE

LUNG TUMORS: 17.0%
LUNG EMPHYSEMA: 6.4%
HYPERPLASIA OF BLADDER EPITHELIUM: 2.1%

R. Balansky et al., Carcinogenesis 30, 1398-1401, 2009
EXPRESSION OF 4858 GENES IN MOUSE LUNG
A. Izzotti et al., Mutat. Res. 591, 212–223, 2005

SMOKE-FREE MICE

SMOKE-EXPOSED MICE

SAFETY

EFFICACY
EFFECT OF CIGARETTE SMOKE (ECS) AND CHEMOPREVENTIVE AGENTS ON miRNA EXPRESSION IN RAT LUNG

EXPOSURE OF HAIRLESS MICE TO HALOGEN LAMPS
SKIN CARCINOGENICITY OF HALOGEN LAMPS

S. De Flora & F. D’Agostini, Nature 356, 569, 1992
F. D’Agostini & S. De Flora, Cancer Res. 54, 5081–5, 1994
MODULATION OF LIGHT-INDUCED SKIN TUMORS BY N–ACETYLCYSTEINE (NAC) AND ASCORBIC ACID (ASA)

F. D’Agostini et al., Carcinogenesis 26, 657–664, 2005

**Incidence (%)**

- Contr.  
- Light  
- Light + NAC  
- Light + ASA  
- Light + ASA + NAC

**Multiplicity (mean ± SE)**

- Contr.  
- Light  
- Light + NAC  
- Light + ASA  
- Light + ASA + NAC

\[P < 0.001, \text{ as compared with Light; } \quad P < 0.001, \text{ as compared with Light + AsA}\]
### The Prevention of Infection–Associated Cancers (S. De Flora and P. Bonanni, 2010)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>IARC Group</th>
<th>Main associated cancer</th>
</tr>
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<tbody>
<tr>
<td><strong>Hepatitis viruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>1</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>1</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HDV</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td><strong>Papillomaviruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α HPV type 16</td>
<td>1</td>
<td>Cancers at several sites</td>
</tr>
<tr>
<td>α HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59</td>
<td>1</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>α HPV type 68</td>
<td>2A</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>α HPV types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 97</td>
<td>2B</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>β HPV type 5 and 8</td>
<td>2B</td>
<td>Skin cancer</td>
</tr>
<tr>
<td>α HPV type 6 and 11</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Other β and γ HPV types</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td><strong>Polyomaviruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JCV</td>
<td>NA</td>
<td>CNS tumors and colorectal cancer?</td>
</tr>
<tr>
<td>MCV</td>
<td>NA</td>
<td>Skin cancer (Merkel cell carcinoma)</td>
</tr>
<tr>
<td>SV40</td>
<td>NA</td>
<td>Malignant mesothelioma? ?</td>
</tr>
<tr>
<td><strong>Herpesviruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV or HHV4</td>
<td>1</td>
<td>Burkitt’s lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppressor-related non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, nasopharyngeal carcinoma, Kaposis sarcoma, primary effusion lymphoma</td>
</tr>
<tr>
<td>KSHV or HHV8</td>
<td>1</td>
<td>Kaposis sarcoma, primary effusion lymphoma</td>
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### Infectious agents cause 17% of all cancers worldwide, 26% in developing world, 8% in developed world

D.M. Parkin, Int.J.Cancer 15, 3030-44, 2005
# The Prevention of Infection–Associated Cancers

(S. De Flora and P. Bonanni, 2010)

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<tr>
<td>HBV</td>
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<td></td>
<td>4.9% of all cancers</td>
</tr>
<tr>
<td>HCV</td>
<td></td>
<td></td>
<td>85.5% of all HCCs</td>
</tr>
<tr>
<td>HDV</td>
<td></td>
<td></td>
<td>5.2% of all cancers</td>
</tr>
<tr>
<td><strong>Papillomaviruses</strong></td>
<td></td>
<td></td>
<td>100% of cervix cancers</td>
</tr>
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<td>Kaposi's sarcoma, primary effusion lymphoma</td>
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<tr>
<td><strong>Retroviruses</strong></td>
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<td></td>
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<tr>
<td>HTLV-I</td>
<td>1</td>
<td>Adult T-cell leukemia/lymphoma</td>
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</tr>
<tr>
<td>HTLV-II</td>
<td>3</td>
<td>None</td>
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<tr>
<td>HIV-I</td>
<td>1</td>
<td>Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, cervical cancer, anus cancer, conjunctive cancer</td>
<td></td>
</tr>
<tr>
<td>HIV-II</td>
<td>2B</td>
<td>Kaposi's sarcoma, non-H Hodgkin's lymphoma</td>
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<tr>
<td>HERV-K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Helicobacter pylori</strong></td>
<td></td>
<td></td>
<td>5.5% of all cancers</td>
</tr>
<tr>
<td><strong>Schistosomes</strong></td>
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<td>63.4% of stomach cancers</td>
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<td>S. haematobium</td>
<td>1</td>
<td>Urinary bladder cancer</td>
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<tr>
<td>S. japonicum</td>
<td>2B</td>
<td>Colorectal and liver cancers</td>
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<td>S. mansoni</td>
<td>3</td>
<td>None</td>
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<tr>
<td><strong>Liver flukes</strong></td>
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<td>Opistorhics viverrini</td>
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<td>Cholangiocarcinoma</td>
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<tr>
<td>Opistorhics felineus</td>
<td>3</td>
<td>None</td>
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<tr>
<td>Chelonchis sinensis</td>
<td>1</td>
<td>Cholangiocarcinoma</td>
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S. De Flora et al, Cancer Res. 47, 4052–8, 1987; Carcinogenesis 10, 1099–1106, 1989
HUMAN ABDOMINAL AORTA WITH ATHEROSCLEROTIC LESIONS

Extraction of DNA from smooth muscle cells
The levels of $^{32}$P postlabelled DNA adducts in the aorta from 85 atherosclerotic patients were significantly correlated with:

- Age of patients
- Number of cigarettes smoked currently
- High blood pressure
- Blood triglycerides
- Blood cholesterol (total/HDL)
- SFS-positive DNA adducts
- Oxidative DNA damage (8-OH-dG)
MODULATION OF DNA ADDUCTS BY DIETARY AGENTS IN THE AORTA OF SMOKE-EXPOSED RATS


DNA adducts/10^8 nucleotides

SHAM
ECS
ECS + 5,6-BF
ECS + D3T
ECS + PEITC
ECS + NAC
ECS + OPZ
ECS + NAC + OPZ

P < 0.01
P < 0.01
P < 0.01
8-oxo-dG DNA ADDUCTS
MODULATION OF DNA ADDUCTS BY DIETARY AGENTS IN THE HEART OF SMOKE-EXPOSED RATS

S. De Flora and A. Izzotti, Mutat. Res., 2009
TERTIARY PREVENTION (Treated cancer patients)

EARLY INTERVENTION (Cancer patients in preclinical or early stage)

PREVENTION OF PROGRESSION (Individuals affected by precancerous lesions)

TARGETED CHEMOPREVENTION (High risk individuals)

PUBLIC HEALTH INTERVENTION (Healthy subjects in the population)

S. De Flora et al., IARC Sci. Publ. No. 139, 1996, pp. 291-301
### PHASE II CHEMOPREVENTION TRIAL WITH NAC IN DUTCH SMOKERS

<table>
<thead>
<tr>
<th></th>
<th>DNA adducts/10^8 nucleotides in BAL cells</th>
<th>8-oxo-dGuo/10^5 nucleotides in BAL cells</th>
<th>Micronuclei in mouth cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td>T₀: 6.0 ± 0.7</td>
<td>4.8 ± 0.5</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>T₆: 5.9 ± 0.7</td>
<td>3.2 ± 0.8</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td><strong>NAC</strong></td>
<td>T₀: 6.0 ± 0.9</td>
<td>4.9 ± 0.7</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>T₆: 4.3 ± 0.8</td>
<td>1.8 ± 0.3</td>
<td>0.9 ± 0.3</td>
</tr>
</tbody>
</table>

Statistically significant as compared to T₀

F.J. van Schooten et al., Cancer Epidem. Biomarkers Prev. 11, 167-175, 2002
PHARMACOGENOMICS / NUTRIGENOMICS OF CHEMOPREVENTIVE AGENTS

Before NAC
All subjects

0.4
0.8
1.2
1.6
2.0
2.4

6 months after NAC

MN (%)

0
0.4
0.8
1.2
1.6
2.0
2.4

NAT2

All subjects

Fast

Slow

GSTM1

+ Null

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