Mechanisms of Multistage Carcinogenesis: Relevance to Bioactive Food Components

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Cancer: Multiple Causative Factors

**Endogenous**
- Acquired
  - Age
  - Prior Exposures
  - ROS
- Genetic
  - Gender
  - Polymorphisms

**Environmental**
- Cig. Smoke
- Env./Occup.
- Chemicals
- Radiation
- Physical agents
- Dietary factors
- Lifestyle
- Microbes
Chemoprevention: Use of agents to inhibit, reverse or retard tumorigenesis

Initiation (1-2 d) → Promotion (> 10 yrs) → Progression (> 1 yr)

Cancer-blocking agents

Cancer-suppressing agents
Genetic and Epigenetic Mechanisms
Carcinogen → Phase I → Electrophile → Phase II → Detoxification

1.  
2.  
3.  
4. ROS → DNA Damage → Mutation → Cancer
5.  

(1-5 indicate potential sites of action of specific bioactive compounds)
Categories of genes targeted during multistage carcinogenesis

*Intracellular Circuitry*
- Agonist-induced signal transduction
- DNA replication and repair
- Cell cycle control
- Cell fate: survival, differentiation, senescence, and apoptosis

*Cell surface and extracellular functions*
- Adhesion molecule; proteases; angiogenic factors, etc
Protective Components in Diet

1. Fruit and Vegetables: Phytochemicals
2. Fiber – colorectal cancer
3. Micronutrients: Vit A, C, E, retinoids, folate
4. Minerals: Calcium – colorectal cancer
   Selenium – Prostate cancer
# Bioactive Food Components that Cause Cancer

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxin</td>
<td>Mold/grains</td>
</tr>
<tr>
<td>Heterocyclic amines</td>
<td>Grilled meat</td>
</tr>
<tr>
<td>PAHs</td>
<td>&quot;</td>
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<tr>
<td>Acrylamide</td>
<td>Fried foods</td>
</tr>
<tr>
<td>Pesticides</td>
<td>Fruits, vegetables</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Water</td>
</tr>
</tbody>
</table>

Except for pesticides all of these compounds are genotoxic.
Bioactive Food Components that have Anticancer Activity in Experimental Systems*

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyphenolic Compounds</td>
<td>EGCG</td>
<td>green tea</td>
</tr>
<tr>
<td></td>
<td>Curcumin</td>
<td>turmeric</td>
</tr>
<tr>
<td></td>
<td>Resveritrol</td>
<td>grapes, peanuts</td>
</tr>
<tr>
<td>Isoflavones</td>
<td>Genistein</td>
<td>Soy</td>
</tr>
<tr>
<td>Isothiocyanates</td>
<td>PEITC</td>
<td>Crucif. Veg.</td>
</tr>
<tr>
<td>Indoles</td>
<td>Indole-3-carbinol</td>
<td>Brassica veg.</td>
</tr>
<tr>
<td>Organosulfur cmpds</td>
<td>SAMC</td>
<td>garlic</td>
</tr>
<tr>
<td>Carotenoids</td>
<td>Lycopene</td>
<td>tomatoes</td>
</tr>
<tr>
<td>Vitamins**</td>
<td>A, C, E, D, FA</td>
<td>various foods</td>
</tr>
<tr>
<td>Minerals**</td>
<td>Se, calcium</td>
<td></td>
</tr>
</tbody>
</table>

* Although epidemiologic data are suggestive for some of these compounds, none have been established as anticancer agents in humans

** Also nutrients
Cellular and Molecular Effects of Bioactive Phytochemicals

1. Antioxidant activity

2. Modulate xenobiotic metabolizing enzymes - carcinogen activation/detoxification

3. Affect signaling molecules and gene expression: cell cycle, cell prolif., differentiation, hormone activity, apoptosis, angiogenesis, inflammation
Molecular Targets of EGCG and Poly E

EGCG | Poly E

EGFR | EGFR | EGFR | HER2

Ras GTP | PKC | PI3K

Raf-1 | MEKK | NIK | Akt

MEK | SEK | Bad | IKK

ERK | JNK | Bcl-xL | NF-κB

Anti-apoptosis | NF-κB

Growth Inhibition and Apoptosis

G1 Phase Arrest

Nucleus

c-fos | c-jun | NF-κB

ELK | AP-1 | Gene Expression

Cyclin D1

Cytoplasm

HER2 | EGFR

Membrane
Future Directions/Methods

Preclinical Studies

Cell culture assays for anticancer effects
  Efficacy, potency
  Mechanisms of action
  Reveal biomarkers

Rodent models – including genetically engineered mice, and biomarkers

Randomized Clinical Trials
  High risk populations
  Precursor lesions
  Pharmacokinetics
  Biomarker
Biomarkers

Markers of oxidative damage: $8\text{-OHdG}$, $F_2\text{-isoprostane}$

DNA adducts: BP-DNA

Serum markers: IGF1, IGFBP-3


Examples: lycopene decreases serum IGF1 (Voskuil, et al., 2005); Vit C plus E decreases BP-DNA in cig. smokers (Mooney et al., 2005).
Interactions Between Bioactive Foods and Hereditary Factors – Nutrigenomics

Polymorphisms/SNPs in antioxidant, DNA repair, drug metabolism, and folate metabolism genes.

Examples: High blood levels of antioxidants reduce prostate cancer risk 10-fold in men with specific SNP in MnSoD gene (Li, et al., Cancer Res., 2498, 2005). A specific SNP in XRCC1 in association with high intake fruits and veggies may decrease breast cancer risk (Shen, et al., CEBP 14, 336, 2005).
Bioactive Compounds – General Issues

Effects of dose
Metabolism
Potential toxicity
Interactions with other bioactive compounds, nutrients, drugs, cigs, other environ. agents
Special populations vs. general public
Effects on other diseases
Bioactive Compounds – Common Themes in Cancer and Cardiovascular Disease

- Multistep process and long latent period
- Multifactor Causation
- Gene/Environment Interactions
- Cigarette smoke
- Role of inflammation
- Role of ROS
- Shared pathways of signal transduction and gene expression
- Certain bioactive compounds may prevent both diseases, i.e., polyphenolic compounds