This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike License. Your use of this material constitutes acceptance of that license and the conditions of use of materials on this site.
Environmental Carcinogenesis

James D. Yager, PhD
Bloomberg School of Public Health
Carcinogenic Process

Classical epidemiology

Population exposed to carcinogen
Pathway to disease
Mechanisms?
Exposure increases cancer risk
Disease

Molecular epidemiology

Carcinogen enters body
Pathway to disease
Markers of susceptibility
Metabolism ↓ Antioxidants Inefficient DNA repair Inefficient immune recognition
Markers of cancer-related changes
Damage to DNA Mutation of a specific gene Abnormal cell growth
Detectable disease appears

Adapted by CTL from Scientific American, May, 1996.
Lecture Outline

Cancer

• A - What Causes It?

• B – Where Does It Occur & What Is It

• C – Mechanisms – Multiple Stages

• D – Genes Whose Mutation Can Lead To Initiation

• E – Promotion and Progression

• F – Lung Cancer
Section A

Cancer - What causes it?

• Gene-Environment Interaction
  ➢ Epidemiological evidence for a role of environment/life-style and endogenous factors
  • Historical perspective
  • Prevalence differences
  • Carcinogenic “Agents”
Historical Perspective

- **1713: Ramazzini**
  - Nuns exhibited a higher frequency of breast cancer; attributed to celibate life
- **1761: Hill**
  - Associated the use of tobacco snuff with cancer of the nasal passages
- **1775: Pott**
  - Noted the occurrence of soot-related cancer in chimney sweeps
- **1894: Unna**
  - Associated sunlight exposure with skin cancer
- **1895: Rehn**
  - Associated occupational exposure to aromatic amine dyes with bladder cancer
- **1915: Ichikawa**
  - First experimental production of tumors in animals (application of coal tar to ears of rabbit)
Incidence Differences

Migrant Populations Assume the Cancer Incidence of Their New Environment Within One to Two Generations

Incidence Differences

- “Cancer occurs in every country..” BUT “…there are wide geographic variations in incidence”* rates
  - See GLOBOCAN 2008 (http://globocan.iarc.fr/)
    • ASR(W) = Age – World Standardized Incidence Rate
  - Incidences of specific tumor types can vary up to several hundred-fold
- There are large differences in tumor incidences within populations of a single country


Winn, D.M. Nature Reviews – Cancer, 5/12, 986, 2005
The Causes of Cancer
Quantitative Estimates of Avoidable Risks of Cancer in the United States

By comparing cancer incidence in the U.S. and the lowest incidence areas of the world, Doll and Peto concluded that:
- 80% of male cancers and 77% of female cancers are potentially avoidable
Carcinogenic Agents

**Exogenous Chemicals**
- **Inorganic:**
  - Arsenic, cadmium, chromium, nickel, etc.
- **Organic:**
  - Polycyclic aromatic hydrocarbons, chlorinated hydrocarbons, heterocyclic amines, aflatoxin, benzene, nitrosamines, formaldehyde, etc.
- **Hormones:**
  - Diethylstilbestrol, ethinyl estradiol, tamoxifen, HRT (equine estrogen equilenin + progestin), etc.

**Endogenous Agents**
- **Estrogen:**
  - breast, prostate
- **Immune system – function/dysfunction**

**Physical agents**
- **X-rays:**
  - breast, leukemia
- **Ultraviolet light:**
  - skin: non-melanoma and melanoma
- **Asbestos:**
  - lung

**Biological agents**
- **Bacteria**
  - *Helicobacter pylori* (Ex.: Stomach cancer)
- **Viruses**
  - RNA tumor viruses
    - Human T-cell leukemia virus —HIV/HTLV)
  - DNA tumor viruses
    - Hepatitis B and C: liver cancer;
    - Papilloma viruses: cervical cancer;
    - Epstein-Barr virus: Burkitt’s lymphoma
### Etiologies of the World’s Leading Cancers*

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Infection</th>
<th>Inflammation</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung/Bronchus</td>
<td>probably</td>
<td></td>
<td>smoking</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td>estrogens, diet</td>
</tr>
<tr>
<td>Colon/Rectum</td>
<td>definitely</td>
<td></td>
<td>diet</td>
</tr>
<tr>
<td>Stomach</td>
<td><em>H. pylori</em></td>
<td>definitely</td>
<td>diet</td>
</tr>
<tr>
<td>Liver</td>
<td>Hep. viruses</td>
<td>definitely</td>
<td>diet (aflatoxin B$_1$)</td>
</tr>
<tr>
<td>Prostate</td>
<td>probably</td>
<td></td>
<td>diet, androgens? estrogen?</td>
</tr>
<tr>
<td>Uterine Cervix</td>
<td>HPV</td>
<td>probably</td>
<td>smoking</td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
<td>maybe</td>
<td>smoking, diet</td>
</tr>
<tr>
<td>Bladder</td>
<td><em>S. haematobium</em></td>
<td>maybe</td>
<td>smoking</td>
</tr>
</tbody>
</table>

| All sites         | often              | almost always    | almost always                |

(excluding skin)

*Ordered by incidence as reported by the World Health Organization
International Agency for Research on Cancer (IARC); see www.iarc.fr

more than 70% of all cancer cases can be prevented
Proportion of Cancer Deaths Estimated to be Attributed to Environmental Influences

- **Tobacco**: 30% (25-40%)
- **Diet**: 35% (10-70%)
- **Biological/Infectious agents**: 30% (25-40%)
- **Unknown**: ?%
- **Geophysical factors**: 3%
- **Medicines & medical procedures**: 1%
- **Pollution**: 2%
- **Occupation**: 4%
- **Reproductive & sexual behavior**: 7% (1-13%)
- **Food additives**: <1%

What Causes Cancer?

- Breathing
- Eating
- Drinking
- Sex
- Doctors
- Parents
Key Points - Section A

- Cancer is a consequence of gene-environment interactions
  - Historical examples of specific exposures/specific cancers
  - Migrant populations assume cancer rate of new location
  - Large differences in incidence within regions of a country
  - Chemicals, viruses, and radiation can be carcinogenic
  - Key environmental factors include diet, smoking/env tobacco smoke, infectious agents
  - Endogenous factors also contribute to cancer

- Environmental factors may contribute to 3/4 of all human cancers
Section B

Cancer

Where Does It Occur?

What Is It?
Major Diseases and Conditions of the World
Disability-Adjusted Life-Years (Billions)

Disability-adjusted life-years (billions)

- 1. Mental illness
- 2. Injuries
- 3. Cardiovascular conditions
- 4. Perinatal conditions
- 5. HIV infection or AIDS
- 6. Sensory organ diseases
- 7. Cancer
- 8. Diarrheal diseases
- 9. Respiratory diseases
- 10. All other noncommunicable diseases

Adapted by CTL from Andersen, NEJM, 2007.
Major Diseases and Conditions of the World
Deaths (Millions)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Deaths (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular diseases</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
</tr>
<tr>
<td>Injuries</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>4</td>
</tr>
<tr>
<td>HIV infection or AIDS</td>
<td>5</td>
</tr>
<tr>
<td>Perinatal conditions</td>
<td>6</td>
</tr>
<tr>
<td>Digestive diseases</td>
<td>7</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>8</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>9</td>
</tr>
<tr>
<td>All other noncommunicable diseases</td>
<td>10</td>
</tr>
<tr>
<td>All other communicable diseases</td>
<td></td>
</tr>
</tbody>
</table>

Annual Age-Adjusted Cancer Incidence Rates for Selected Cancers, Males, United States, 1975-2006

Adapted by CTL from CA CANCER J CLIN 2010;60:277-300.
Annual Age-Adjusted Cancer Death Rates for Selected Cancers, Males, United States, 1930-2006

21% decrease for men in death rates for all cancers since 1990

Adapted by CTL from CA CANCER J CLIN 2010;60:277-300.
Annual Age-Adjusted Cancer Death Rates for Selected Cancers, Females, United States, 1930-2006

12% decrease for women in death rates for all cancers since 1990

Adapted by CTL from CA CANCER J CLIN 2010;60:277-300.
Cancer

- What is it?
  - Group of diseases
  - Uncontrolled growth
  - Spread (invasion, metastasis)
  - Multiyear process

![Diagram showing the progression of cancer from normal to initiated, then to precancerous stages, and finally to cancer stages.](image)
Key Points – Section B

- Rising cancer incidence is a global problem
- US cancer incidence and death rates for a number of cancer sites is declining
- Cancer is a group of diseases characterized by uncontrolled growth and progression from pre-cancer to invasive, malignant cancer
- Development of a malignant tumor can take 10-20 years making attribution of cause to effect difficult

Continued
Section C

Mechanisms of Carcinogenesis

Multiple Stages:
Initiation
Promotion
Progression
Multistage Carcinogenesis

- **Initiation:**
  - somatic cell mutation

- **Promotion:**
  - clonal expansion of initiated cells

- **Progression:**
  - evolution of neoplastic phenotype due to continued mutation, chromosome aberrations and/or epigenetic changes

  - angiogenesis, invasiveness, metastasis
Carcinogenesis: A Progressive, Multistage Process

Initiation
- Activation of proto-oncogenes
- Inactivation of tumor suppressor genes
- Inactivation of genomic stability genes

Promotion
- Defects in terminal differentiation
- Defects in growth control
- Resistance to cytotoxicity
- Defects in programmed cell death

Progression
- Accumulation of additional mutations
- Additional epigenetic changes

Adapted by CTLT from Curtis Harris, from modification by Groopman & Yager.
Initiation and Promotion Operational Definitions

No Tumors

- Initiator
- Promotor

Many Tumors

Photos by Tom Kensler
Initiation

- Molecular target: DNA
  - Carcinogen metabolism -> Activation -> DNA damage
  - DNA repair processes

- Gene targets:
  - Proto-oncogenes
  - Tumor suppressor genes
Chemical & Physical Agents that cause DNA damage are referred to as being Genotoxic

A hallmark of cancer is **genetic instability** at the nucleotide and/or chromosomal level

**DNA Damage ->**

- **Mutation** (mutagenesis)
  - “Point” or “gene-locus” mutation (base pairs), substitution, and small deletions or additions
- **Chromosome breaks** (Clastogenesis)
  - Results in gain, loss, or rearrangement of pieces of chromosome
- **Chromosome Number change** (Aneuplody)
  - Gain or loss of one or more chromosomes
Types of DNA Damage

- Specific Binding
- Base Alteration
- Single Strand Break
- DNA-Protein Crosslink
- Intra Protein Crosslink
- Base Detachment A
- Apurinic Site
- Double Strand Break
- Intercalation
- Intra-Strand Crosslinks
- T(OH)₂
Specific Sites for Carcinogen-DNA Base Adducts

I. Alkylating Agents, Mycotoxins, estradiol
II. Aromatic Amines, oxidative damage
III. Polycyclic Aromatic Hydrocarbons, Alkenylbenzenes
IV. Methylating & Ethylating Agents
DNA Repair Processes

- Replication errors
  - Proofreading during replication
  - Mismatch repair
- Damage caused by endogenous and exogenous agents
  - Direct damage reversal
  - Base excision repair
  - Nucleotide excision repair
Nucleotide Excision Repair

1. Damage-specific DNA incising activity (2 nicks)

2. Oligonucleotide excision

3. A Polymerase + DNA ligase
Correlation Between DNA Repair Capacity & Mutagen Sensitivity

Adapted from Wei et al. Cancer Epi. Biomarkers & Prev. 5:199-204 (1996); slide provided by J. Groopman
Key Points – Section C

- Carcinogenesis is a multistage process
- Initiation caused by mutation is irreversible
- DNA is a major target for carcinogens
- Damage may cause mutation leading to gain or loss of function of key genes
- A variety of DNA repair processes protect the cell from DNA damage caused by exogenous and endogenous agents
- DNA repair capacity correlates with sensitivity to mutation
- A hallmark of cancer is genetic instability
Section D

Genes whose Mutation can lead to Initiation
## Single Genes and Susceptibility Genes—and Cancer Risk

<table>
<thead>
<tr>
<th></th>
<th>Single genes</th>
<th>Susceptibility genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Necessary and sufficient for disease causation</td>
<td>Alter risk—but is neither necessary or sufficient for disease causation</td>
</tr>
<tr>
<td><strong>Example</strong></td>
<td><em>BRCA</em> (breast/ovary) <em>APC</em> (polyposis coli) <em>RB</em> (retinoblastoma)</td>
<td><em>CYP1A1</em> (lung) <em>CYP2D6</em> (lung) <em>GST-M1</em> (lung, bladder) <em>DNA repair genes</em></td>
</tr>
<tr>
<td><strong>Gene prevalence</strong></td>
<td>Low</td>
<td>Often high</td>
</tr>
<tr>
<td><strong>Gene type</strong></td>
<td>Mutation</td>
<td>Mutation</td>
</tr>
<tr>
<td><strong>Study setting</strong></td>
<td>Family</td>
<td>General population/epidemiological studies</td>
</tr>
<tr>
<td><strong>Strength of association</strong></td>
<td>Very high</td>
<td>Low to moderate</td>
</tr>
<tr>
<td><strong>Absolute risk</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Population attributable risk</strong></td>
<td>Low</td>
<td>High (because mutation common)</td>
</tr>
<tr>
<td><strong>Gene-environment interaction/exposure</strong></td>
<td>Secondary and variable</td>
<td>Primary and crucial</td>
</tr>
</tbody>
</table>
Two Categories of Genes in which “Mutation” is Associated with Cancer

❖ Gain of function:
  – Proto-oncogenes become oncogenes
    • Point mutation – change in amino acid sequence
    • Translocation – gene or part of gene moved to another location
    • Amplification – multiple copies of gene created

❖ Loss of Function
  – Tumor suppressor genes lose function
    • Deletion
    • Translocation
    • Mutation
Oncogenes

- Presence of proto-oncogenes in normal cells
- Detection of activated proto-oncogenes (oncogenes) in tumor cells
  - Ras gene – one of the first discovered using transfection
# Oncogenes Genes

## Selected Examples with Function & Location

Contribute to tumor formation when expression/function enhanced

### Selected Examples*

<table>
<thead>
<tr>
<th>Genes</th>
<th>Functions</th>
<th>Associated Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Src</td>
<td>Cytoplasmic Tyrosine Kinase</td>
<td>Sarcomas</td>
</tr>
<tr>
<td>ras</td>
<td>G-protein; Signal transduction</td>
<td>Bladder</td>
</tr>
<tr>
<td></td>
<td>rasH</td>
<td>Lung, Ovarian, Bladder</td>
</tr>
<tr>
<td></td>
<td>rasK</td>
<td>Breast</td>
</tr>
<tr>
<td>rasN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myc</td>
<td>Cell Proliferation and DNA Synthesis</td>
<td>Neuroblastoma, Retinoblastoma</td>
</tr>
<tr>
<td></td>
<td>mycN</td>
<td>Breast, leukemia, Lung, Cervical, Colon</td>
</tr>
<tr>
<td></td>
<td>mycC</td>
<td></td>
</tr>
<tr>
<td>EGF Family</td>
<td>Membrane Receptor the stimulates DNA Synthesis</td>
<td>Breast, Salivary Gland, Ovarian</td>
</tr>
<tr>
<td>Erb-2/</td>
<td>Synthesis – a Tyrosine Kinase</td>
<td></td>
</tr>
<tr>
<td>Her2/neu</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Cancer Quest – Tumor Suppressors, Emory University, 2008; accessed Aug, 2011
Oncogenes Drive Tumorigenesis


Impact of *erB2/neu* Amplification on Breast Cancer

### Tumor Suppressor genes – Selected Examples

<table>
<thead>
<tr>
<th>Genes</th>
<th>Functions</th>
<th>Associated Cancers</th>
</tr>
</thead>
</table>
| P53   | - Transcription factor regulating genes controlling cell division and cell death  
- Sensor of DNA damage  
- Aids in decision between repair and activation of programmed cell death | Bladder, Breast, Liver, Colorectal, Lung, Prostate |
| Rb    | - Signal integrator related to cell cycle progression  
- Transduces growth inhibitory signals | Retinoblastoma, Sarcomas, Bladder, Breast, Lung |
| BRCA  | - Involvement in DNA repair  
- Regulation of gene expression | Inherited Breast and Ovarian |
| APC   | - Controls activity of certain transcription factors | Familial adenomatous & non-inherited colorectal cancers |

Adapted from Cancer Quest – Tumor Suppressors, Emory University, 2008; accessed Aug, 2011
P53 Mutations in Cancer

Adapted by CTL from The Biology of Cancer, Garland Science 2007.
P53 Mutations in Lung Tumors

- Smokers (n=459)
- Nonsmokers (n=160)
- Smoky coal (n=21)
- All cancers (n=15,121)

P53 Mutations in Lung Tumors

Smokers

Nonsmokers

Smoky coal

All cancers

p53 Mutations in Liver Tumors from Different Regions of the World

*G:C to T:A mutation a hallmark of Aflatoxin exposure

## Genetic Model for Colorectal Tumorigenesis

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>5q</th>
<th>12p</th>
<th>18q</th>
<th>17p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteration</td>
<td>Loss</td>
<td>Activation</td>
<td>Loss</td>
<td>Loss</td>
</tr>
<tr>
<td>Gene</td>
<td>APC</td>
<td>k-ras</td>
<td>DCC</td>
<td>p53</td>
</tr>
<tr>
<td>Normal epithelium</td>
<td>Hyperproliferative epithelium</td>
<td>Early adenoma</td>
<td>Intermediate adenoma</td>
<td>Late adenoma</td>
</tr>
</tbody>
</table>

Adapted by CTLT from Vogelstein & Kinsler, 1993.
Whole Exome Sequences of 100 Human Cancers*

- 11 colorectal cancers
- 11 breast cancers
- 24 pancreas cancers
- 22 gliomas
- 22 medulloblastomas
- 2 leukemias
- 1 breast cancer
- 1 breast cancer
- 4 granulosa cell tumors
- 1 lung cancer Sanger
- 1 melanoma

- 3142 mutated genes
- 286 tumor suppressors
- 33 oncogenes

*Vogelstein B AACR Annual Meeting (2010) – Slide provided by W. Nelson
Mutation Spectra in Colon and Breast Cancer

Colan Tumor

Breast Tumor

- Single gene mutation
- Multiple mutations in particular gene

Adapted by CTL from Wood et al., Science 318, 1108 (2007).
Adapted by CTL from Wood et al., Science 318, 1108 (2007).
Hallmarks of Cancer

- Avoiding immune destruction
- Evading growth suppressors
- Activating invasion & metastasis
- Tumor-promoting inflammation
- Enabling replicative immortality
- Inducing angiogenesis
- Resisting cell death
- Sustaining proliferative signaling
- Deregulating cellular energetics
- Genome instability & mutation

Emerging Hallmarks

Adapted by CTL from Weinberg, RA, Cell, 2011.
Key points – Section D

- Inherited genetic susceptibility can increase risk
  - Mutations in key genes can lead to high individual risk, but low attributable population risk
  - Mutations in certain genes lead to lower individual risk but high attributable population risk

- Oncogenes and tumor suppressor genes are key molecular/biological targets

- Tumors contain hundreds of mutations and contain a few common mutations
Key Points – Section D cont’d

- Mutations accumulate as progression occurs
- Different carcinogens cause different mutations – “finger print”
  - Adducts of chemicals with DNA bases can serve as biomarkers of biologically effective dose
Section E

Multistage Nature of Carcinogenesis

Promotion & Progression
Not all carcinogens are mutagenic
Initiation and Promotion of Mouse Skin Carcinogenesis

Photos by Tom Kensler
### Neoplasms Associated with Prolonged Contact with Promoting Agents in the Environment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Resulting neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary fat</td>
<td>Mammary adenocarcinoma</td>
</tr>
<tr>
<td>High caloric intake</td>
<td>Increased cancer incidence in general</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td>Bronchogenic carcinoma, esophageal and bladder cancer</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Bronchogenic carcinoma, mesothelioma</td>
</tr>
<tr>
<td>Halogenated hydrocarbons (dioxin, PCBs)</td>
<td>Liver</td>
</tr>
<tr>
<td>Phorbol esters</td>
<td>Esophageal cancer (?)</td>
</tr>
<tr>
<td>Saccharin</td>
<td>Bladder cancer *</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Liver *</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Mammary adenocarcinoma</td>
</tr>
<tr>
<td>Synthetic estrogens</td>
<td>Liver adenomas</td>
</tr>
<tr>
<td>Alcoholic beverages</td>
<td>Liver and esophageal cancer</td>
</tr>
</tbody>
</table>

*Promotion demonstrated in experimental animals, but not in humans*
**Promoters Can Determine the Target Site for Tumors**

<table>
<thead>
<tr>
<th>Initiator</th>
<th>Tumor Promoter</th>
<th>Target Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Acetylaminofluorin (AAF)</td>
<td>Phenobarbital</td>
<td>Liver</td>
</tr>
<tr>
<td></td>
<td>Saccharin</td>
<td>Bladder</td>
</tr>
<tr>
<td>N-methylnitroso-urea (MNU)</td>
<td>Phenobarbital</td>
<td>Liver and thyroid</td>
</tr>
<tr>
<td></td>
<td>Saccharin</td>
<td>Bladder</td>
</tr>
</tbody>
</table>
How Do Promoters Work?

- Mechanisms for selection and clonal expansion by tumor promoters
  - Differential effects on initiated vs. “normal” cells in tissue
Relative Risk for Developing Lung Cancer
Compared with the Risk of Dying from Lung Cancer for a Nonsmoker not Exposed to Asbestos

Source: Report of the Surgeon General, 1985
Tumor Progression

- Conversion from benign tumor to malignancy
- DNA-damaging agents cause progression
  - Alkylating agents (mutagens)
  - \( \text{H}_2\text{O}_2 \) and organic peroxides
  - Radiation
- Chemicals/agents that cause epigenetic changes may also cause progression
Progression/Malignant Conversion Caused by Benzoyl Peroxide (BzPO)

BzPO
- Free radical generating agent
- Weak promoter
- Inactive as complete carcinogen or initiator

Adapted by CTLT from O'Connell et al., Cancer Research 46:2863, 1986.
Chromatin in Interphase nucleus

- Nuclear membrane
- Chromatin fiber
- Chromatin fiber (10nm)
- H1
- Nucleosomes
- Core histones
  - H3
  - H4
  - H2B
  - H2A
- DNA
- Nuclear pore
- Nuclear matrix

Slide courtesy of Yanming Wang
Center for Eukaryotic Gene Regulation
Department of Biochemistry and Molecular Biology
Penn State University. All Rights Reserved.
**Epigenetics**

- **Epigenetics**: Heritable changes in gene expression caused by mechanisms other than changes in the DNA sequence
  - Methylation at CpG sequences and islands in DNA
  - Modification of histones by methylation and acetylation

A. Normal (open chromatin)

B. Hypermethylation (closed chromatin)

Epigenetic Effects

- Known or suspected agents that cause epigenetic changes include:
  - Heavy metals
  - Pesticides
  - Diesel exhaust
  - Tobacco smoke
  - Polycyclic aromatic hydrocarbons
  - Hormones
    - Endogenous: estradiol
    - Exogenous (endocrine disruptors): bisphenol A (BPA)
  - Nutrients
Key Points – Section E

- Carcinogenesis is a long, multistage process yielding a heterogeneous family of diseases – Cancer
- Promotion is a reversible process whereby initiated cells differentially proliferate in response to promoting agents
- Promoters can exhibit tissue specificity
- Progression is associated with the accumulation of mutations and epigenetic changes leading to evolution of a malignant phenotype
Key Points – Section E

- Epigenetics refers to heritable changes in gene expression
  - Does not involve changes in DNA base sequence
  - Mediated through changes in methylation of cytosines at CpG islands and/or changes in histones that alter the conformation of chromatin
  - Can cause inappropriate suppression of gene expression (tumor suppressor genes?) or increased expression (oncogenes?) and thus contribute to cancer progression
Section F

Lung Cancer
Carcinogenic Process

Classical epidemiology

Population exposed to carcinogen
Pathway to disease
Mechanisms?
Exposure increases cancer risk
Disease

Molecular epidemiology

Carcinogen enters body
Pathway to disease
Markers of susceptibility
Metabolism ↓ Antioxidants Inefficient DNA repair Inefficient immune recognition
Markers of cancer-related changes
Damage to DNA Mutation of a specific gene Abnormal cell growth
Detectable disease appears

Adapted by CTL from Scientific American, May, 1996.
Tobacco use in the US, 1900-2000

*Per 100,000, age-adjusted to 2000 US standard population.
## Chemicals in Tobacco Smoke

### Table 1.13. Yields of IARC carcinogens in the mainstream smoke of Canadian regular size cigarettes — Comparison of ISO and Health Canada machine-smoking parameters

<table>
<thead>
<tr>
<th>Compound</th>
<th>ISO smoking parameters*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regular</td>
</tr>
<tr>
<td><strong>Tar (mg/cig)</strong></td>
<td>13.4</td>
</tr>
<tr>
<td><strong>Nicotine (mg/cig)</strong></td>
<td>1.1</td>
</tr>
<tr>
<td><strong>IARC Group 1</strong></td>
<td></td>
</tr>
<tr>
<td>Benzene (µg/cig)</td>
<td>56.3</td>
</tr>
<tr>
<td>Cadmium (ng/cig)</td>
<td>114.0</td>
</tr>
<tr>
<td>2-Aminonaphthalene (ng/cig)</td>
<td>11.8</td>
</tr>
<tr>
<td>Nickel (ng/cig)</td>
<td>4.0</td>
</tr>
<tr>
<td>Chromium (ng/cig)</td>
<td>5.0</td>
</tr>
<tr>
<td>Arsenic (ng/cig)</td>
<td>BDL</td>
</tr>
<tr>
<td>4-Aminobiphenyl (ng/cig)</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>IARC Group 2A</strong></td>
<td></td>
</tr>
<tr>
<td>Formaldehyde (µg/cig)</td>
<td>60.8</td>
</tr>
<tr>
<td>1,3-Butadiene (µg/cig)</td>
<td>46.6</td>
</tr>
<tr>
<td>Benzo[a]pyrene (ng/cig)</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>IARC Group 2B</strong></td>
<td></td>
</tr>
<tr>
<td>Acetaldehyde (µg/cig)</td>
<td>703.0</td>
</tr>
<tr>
<td>Isoprene (µg/cig)</td>
<td>222.0</td>
</tr>
<tr>
<td>Catechol (µg/cig)</td>
<td>74.5</td>
</tr>
<tr>
<td>Acrylonitrile (µg/cig)</td>
<td>11.9</td>
</tr>
<tr>
<td>Styrene (µg/cig)</td>
<td>10.9</td>
</tr>
<tr>
<td>NNK (ng/cig)</td>
<td>84.4</td>
</tr>
<tr>
<td>NNN (ng/cig)</td>
<td>42.0</td>
</tr>
<tr>
<td>Lead (ng/cig)</td>
<td>15.2</td>
</tr>
</tbody>
</table>

BDL, below detection level; NQ, not quantifiable; NNK, 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosonornicotine

* International Standards Organization/United States Federal Trade Commission test conditions: puff volume, 35 mL; puff interval, 60 sec; puff duration, 2 sec; ventilation holes not blocked

---

## Chemicals in Side-stream Tobacco Smoke

### Table 1.5. Yields of IARC carcinogens in regular-sized Canadian cigarettes. Comparison of International Organization for Standardization (ISO)* and Health Canada (HC)* machine-smoking parameters

<table>
<thead>
<tr>
<th>Compound</th>
<th>ISO smoking parameters</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regular (full flavour)</td>
<td>Light</td>
<td>Extra light</td>
<td>Ultra light</td>
</tr>
<tr>
<td><strong>IARC Group 1 carcinogens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzene (μg/cig.)</td>
<td>222.0</td>
<td>250.0</td>
<td>260.0</td>
<td>296.0*</td>
</tr>
<tr>
<td>Cadmium (ng/cig.)</td>
<td>438.0</td>
<td>484.0</td>
<td>502.0*</td>
<td>627.0*</td>
</tr>
<tr>
<td>2-Aminonaphthalene (ng/cig.)</td>
<td>157.0</td>
<td>147.0</td>
<td>175.0</td>
<td>186.0</td>
</tr>
<tr>
<td>Nickel (ng/cig.)</td>
<td>34.3</td>
<td>45.1</td>
<td>74.4*</td>
<td>73.0*</td>
</tr>
<tr>
<td>Chromium (ng/cig.)</td>
<td>61.0</td>
<td>62.0</td>
<td>121*</td>
<td>82.9*</td>
</tr>
<tr>
<td>Arsenic (ng/cig.)</td>
<td>ND</td>
<td>NQ</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4-Aminobiphenyl (ng/cig.)</td>
<td>22.1</td>
<td>19.5</td>
<td>21.0</td>
<td>21.2</td>
</tr>
<tr>
<td><strong>IARC Group 2A carcinogens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formaldehyde (μg/cig.)</td>
<td>378.0</td>
<td>326.0</td>
<td>414.0</td>
<td>431.0</td>
</tr>
<tr>
<td>1,3-Butadiene (μg/cig.)</td>
<td>196.0</td>
<td>185.0</td>
<td>264.0</td>
<td>299.0</td>
</tr>
<tr>
<td>Benzo[a]pyrene (ng/cig.)</td>
<td>48.8</td>
<td>98.3</td>
<td>92.2</td>
<td>113.0</td>
</tr>
<tr>
<td><strong>IARC Group 2B carcinogens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaldehyde (μg/cig.)</td>
<td>1416.0</td>
<td>1454.0</td>
<td>1449.0</td>
<td>1492.0</td>
</tr>
<tr>
<td>Isoprene (μg/cig.)</td>
<td>1043.0</td>
<td>1164.0</td>
<td>1060.0</td>
<td>1172.0</td>
</tr>
<tr>
<td>Catechol (μg/cig.)</td>
<td>130.0</td>
<td>117.0</td>
<td>149.0</td>
<td>148.0</td>
</tr>
<tr>
<td>Acrylonitrile (μg/cig.)</td>
<td>78.6</td>
<td>85.6</td>
<td>74.1</td>
<td>81.8</td>
</tr>
<tr>
<td>Styrene (μg/cig.)</td>
<td>74.0</td>
<td>84.7</td>
<td>87.5</td>
<td>108.0*</td>
</tr>
<tr>
<td>NNK (ng/cig.)</td>
<td>95.2</td>
<td>153.4</td>
<td>38.3</td>
<td>34.7</td>
</tr>
<tr>
<td>NNN (ng/cig.)</td>
<td>23.3</td>
<td>53.9</td>
<td>43.7</td>
<td>45.2</td>
</tr>
<tr>
<td>Lead (ng/cig.)</td>
<td>54.8</td>
<td>39.4</td>
<td>22.3</td>
<td>18.5</td>
</tr>
</tbody>
</table>

NNN, N’-nitrosonornicotine; NNK, 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butane; ND, not detectable; NQ, not quantifiable
*ISO smoking parameters: 35 mL puff in 2 sec, interval 60 sec, ventilation holes not blocked
*HC: Health Canada smoking parameters: 56 mL puff in 2 sec, interval 26 sec, ventilation holes fully blocked
* Reporting period: year 1999
* Changed according to personal communication with B. Beech, Health Canada
Cotinine in Smoking & Nonsmoking Mothers and Their Children

PAH*-albumin Adducts in Smoking & Nonsmoking Mothers and Their Children

Adapted by CTL from Perera Sci Am May 1996, pp 54-62.

*PAH = polycyclic aromatic hydrocarbon
Key Points – Section F

- It takes 40 years for a decrease in tobacco use to be followed by a decline in tobacco-related cancer
- Tobacco smoke contains many initiators and promoters
- Biomarkers for exposure to tobacco smoke include cotinine and PAH adducts
- Most cancer is, in theory, preventable