UNIVERSITAS CAROLINA PRAGENSIS
Charles University in Prague - First Faculty of Medicine

MOLECULAR CARCINOGENESIS

Physical, chemical and viral carcinogenesis

ÚBEO
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Key words:

- **Oncogenesis**: Pathogenesis of neoplasm (b/m)
- **Carcinogenesis**: Pathogenesis of cancer (m)
- **Carcinogen** – agent causing cancer.
- **Oncogen** – agent causing neoplasm.
- **Mutagen** – agent causing mutation.
- **Oncogenes** – genes causing cancer
- **p-onc, v-onc, c-onc** – Proto/viral/cell → naming of oncogenes.
Cancer Etiology

1. Genetic Predisposition
2. Physical Carcinogenesis
3. Chemical Carcinogenesis
4. Hormone
5. Viral carcinogenesis
6. Trauma and Chronic Inflammation
7. Parasites
Environmental factors damaging DNA:
- physical
- chemical
- biological

Genetic factors:
- mutation in proto-oncogene
- mutation in tumor suppressor gene
- gene affecting DNA repair

Activation of oncogenes
growth-promoting oncogenes

Alterations of apoptosis
regulating genes

Inactivation of tumor suppressor genes

Expression of altered gene products
Loss of regulation product expression

Clonal expansion

Other mutation

Heterogeneity

MALIGNANT TUMOR
Mutation inactivates tumor suppressor gene

CELLS PROLIFERATE

Mutation inactivates DNA repair gene

Mutation of proto-oncogene creates an oncogene

Mutation inactivates several more tumor suppressor genes

CANCER

1. Growth factor

2. Tyrosine-kinase receptor

3. G protein

4. Protein kinases (phosphorylation cascade)

5. Transcription factor (activator)

NUCLEUS

DNA

Gene expression

Protein that stimulates the cell cycle

(a) Growth-stimulating pathway

Protein overexpressed

Cell cycle overstimulated

(b) Growth-inhibiting pathway

Protein absent

Cell cycle not inhibited

(c) Effects of abnormalities (both increase cell division)
(a) Growth-stimulating pathway

1. Growth factor
2. Tyrosine-kinase receptor
3. G protein
4. Protein kinases (phosphorylation cascade)
5. Transcription factor (activator)

(NUCLEUS)
DNA → Gene expression → Protein that stimulates the cell cycle

(b) Growth-inhibiting pathway

1. Growth-inhibiting factor
2. Receptor
3. G protein
4. Protein kinases
5. Transcription factor (such as p53)

DNA → Protein that inhibits the cell cycle

(c) Effects of abnormalities (both increase cell division)

Protein overexpressed: Cell cycle overstressed
Protein absent: Cell cycle not inhibited

Defective or missing transcription factor, such as p53, cannot activate transcription.
Clonal selection of cancer cells
HALLMARKS OF CANCER CELL

Pathogenesis of neoplasma: long-term „multi-stage process“ (8 – 20 years) → accumulation of genetic defects – mutations in protooncogenes and tumor-suppressor genes → advantage of growth and surviving

1. Independence of cell on growth factors and signals restraining growth
   a) self-sufficiency in growth factors
   b) loss of sensitivity to signals for turn-off of growth

2. Loss of contact inhibition of growth → damage of cadherins, integrins – central role in regulation of cellular adhesion and mobility

3. Evading apoptosis → cell immortality
4. Unlimited cell division

5. Increased angiogenesis → production of VEGF

6. Metastasing: degradation of extracellular matrix by metalloproteinases, cell migration, formation of new lymphatic way and expression of receptors for chemokines → „homing“ in specific tissues – magnifying tumor repress surrounding tissues:
   - accumulation next mutations
   - formation of self blood supplementation by increased vascularisation
HALLMARKS OF CANCER CELL

- Self-sufficiency in growth signals
- Evading apoptosis
- Insensitivity to anti-growth signals
- Sustained angiogenesis
- Tissue invasion & metastasis
- Limitless replication potential
MALIGNANT TUMORS

Initiation

Genetic factors
(Oncogenes / tumor suppressor genes)

Promotion

Epigenetic factors
(clonal expansion)

Progression

Mitogenesis
Immune surveillance - escape
Angiogenesis
PARTICIPATION OF TELOMERES AND TELOMERASE ON TUMOR TRANSFORMATION

Telomere shortening
  → Excessive
    → Limited capacity for replication
      → Loss of chromosomal integrity
        → Genetic instability
          → Promotion of malignisation
            → Activation of telomerase
              → Replicational immortality

Telomerase holoenzyme
  → Telomerase inhibition
    → Telomere shortening
      → Signaling for permanent leave of cell cycle
        → Cellular aging
          → APOPTOSIS

Telomerase activation
  → Maintenance of telomeres
    → Signalling for continuation of cell cycle
      → Cell immortality
        → TUMORIGENESIS
Biochemical changes in tumor cells

Tumorogenesis is accompanied with changes in metabolism

- **Metabolic changes:**
  
  - *increased glucose transport and uptake* into cells → overexpression of hypoxia inducible transport proteins with higher affinity to glucose are in cytoplasmic membrane – GLUT1 and GLUT3. The links between hypoxia-induced genes, glucose transporters and angiogenic factors exist.

  - *increased rates of glycolysis* - activation of tumor type hexokinase II expression, phosphorylation of key regulation enzymes – accumulation of lactate – shift glucose metabolism from oxidative phosphorylation to aerobic glycolysis → „**Warburg phenomenon**“.
The oxygen-sensitive transcription factor hypoxia-inducible factor (HIF-1) has come a new understanding of the molecular link between hypoxia and deregulated glucose metabolism.

HIF-1 induces a number of genes integral to angiogenesis, e.g. vascular endothelial growth factor (VEGF), a process intimately involved with metastatic spread.

- increase biosynthesis of purine and pyrimidine nucleotides de novo, including of increased activity of ribonucleotide reductase, thymidylate synthase and thymidine kinase

- activation of DNA and RNA biosynthesis
- secretion of proteases (e.g. matrix metalloproteinases - MMPs, cathepsins, collagenase, elastase etc.)

- decrease of protease inhibitor production

- autocrine secretion of growth factors

- changes in composition of cytoplasmic membrane – cells change a shape

- changes of gene expression – proteins and enzymes characteristic for embryonic cells appear → they may be used as „tumor markers“ in diagnostics

- formation of unusual hormones – in some tumors (e.g. ACTH production in small cell lung carcinoma)

- changes or loss differentiation of biochemical functions
CAUSES OF MALIGNANT TUMORS

A. Influences of environment

1. Physical factors
   
   a) ionizing radiation – formation of \( \cdot \text{OH} \rightarrow \) disjunction \( \rightarrow \) random fusion \( \rightarrow \) mutations
      
      • single stranded breaks
      • double stranded breaks

   b) UV radiation \( \rightarrow \) Py-Py dimmers
UV radiation / malignant tumors of skin

- **UVC** = 100 - 290 nm - **germicidal**
- **UVB** = 280 - 315 nm - **germicidal**
- **UVA** = 315 - 400 nm

\[
\begin{align*}
\text{UVC} & \rightarrow \text{completely absorbed by ozonosphere} \rightarrow \text{harmless} \\
\text{from artificial source} & \text{(germicidal lamps) is harmful!}
\end{align*}
\]

- **UVB** → absorbed by DNA → Py-Py dimers → **skin tumors**
  (carcinoma, basalioma, melanoma)

- **UVA** → possibly is not absorbed by DNA, but it is absorbed by different molecules → free radicals → damage of DNA → **aging and carcinoma of skin**
  - Deletion: CTG → CG and point mutation: e.g. G → T
2. *Chemical factors* = *chemical carcinogens*
   a) *primary carcinogens*
   b) *secondary carcinogens*

3. *Biological factors*
   a) **viruses** – oncogenic DNA and RNA
   b) **bacteria** – *Helicobacter pylori*
   c) **parasites** – *Schistosoma haematobium*

**B. Hereditary causes** – genetic defect in germinal cells

**C. Combination of both** – enviromental factors + inherited defects in genome

**D. Unknown causes**
CHEMICAL CARCINOGENESIS
First evidences of chemical carcinogenesis

1761 – John Hill: nasal tumors after snuff

1775 – Persival Pott: carcinomas of scrotum by chimneysweep

On his findings Guild of Danish chimney sweepers on booted rule: „Every member must bath every day.“

1895 – Rehn: carcinomas of urinary bladder by workers working with aniline dyes

1915 – Yamogiwa and Ichikawa: described carcinomas of rabbit ear skin after repeated painting with coal tar → confirmation of Pott’s observations and first demonstration that a chemical could produce cancer in animals

1930’s – Kennaway, Cook, Hewitt, Hieger: 3,4-benzo[a]pyrene identification in coal tar

1940’s – James and Elizabeth Miller: Relationship between metabolic activation, DNA adduct formation, and tumorigenesis.
Carcinogens:  
1. Inorganic  
2. Organic  
3. Hormones  

Primary carcinogens: active without metabolic activation  
Secondary carcinogens: firstly they must be activated by biotransformation = procarcinogens  
Cocarcinogens: directly increase a carcinogenic effect e.g. with induction of biotransformation enzymes  
Promoters: indirectly increase a carcinogenic effect with stimulation of proliferation
Procarcinogen → detoxification

metabolic activation

Carcinogen → detoxification; bond to other nucleophils

INITIATION bond to DNA

DNA damage → DNA repair

replication

Latent tumor cell

Repair failed

Cells stimulated to growth

PROMOTION (growth)

Tumor formation

PROGRESS

Malignant tumor

PROGRESS

METASTASIZING
CHEMICAL CARCINOGENS

A. Procarcinogens → necessary metabolic activation to „ultimate“ carcinogens

1. Polycyclic aromatic hydrocarbons - PAH
   a) benzanthracene (1st clear carcinogen)
   b) 3,4-benzo[a]pyrene (isolated from coal tar)
   c) 3-methylcholanthrene (prepared from steroids, deoxycholic acid)
   d) 7,12-dimethylbenzanthracene (most efficient carcinogen)

2. Aromatic amines and azo-dyes
   a) 2-naftylamine (causes bladder carcinoma)
   b) 2-acetylaminofluorene (causes hepatomas)
   c) 4-dimethylaminoazobenzene (causes hepatomas)

3. Natural compounds – products of mould and plant
   a) aflatoxin B₁ (effective hepatocarcinogen - A. flavus – occurs in the contaminated foodstuff, e.g. peanuts))
   b) mitomycin C – cytostaticum
Aflatoxin B₃ is metabolized by CYP1A2 and CYP3A4 to Aflatoxin M₃ (urine, milk) through epoxidation.

Aflatoxin B₃-8,9-oxide is further metabolized by GSTs to Aflatoxin-glutathione conjugate (bile) and then to Aflatoxin-N-acetylcysteine (urine).

The DNA adduct is formed by the promutagenic abasic place, leading to Aflatoxin-N7-guanine adduct (urine).
4. Others

a) N-nitrosamines - can arise by action of bacteria to nitrite in food

b) some insecticides (chlordane and others)

c) tetrachlormethane (CCl₄)

d) ethylene oxide – strong carcinogen and mutagen

e) some metals (chromium and nickel)
B. Direct carcinogens → react direct with DNA molecule

1. Alkylating agents
   a) cytostatics and immunosuppressives (cyclophosphamide, busulphane, chlorambucil)
   b) beta-propiolactone
   c) bis-(chloromethyl)-ether

2. Acetylating agents
   a) 1-acetylimidazole
# Carcinogenic Factors in Workplace

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>ENVIRONMENT</th>
<th>LOCALISATION OF TUMOR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical factors</strong></td>
<td>$\gamma$ and UV radiation</td>
<td></td>
</tr>
<tr>
<td>Radon</td>
<td>Some ore mine (uranium), rift - flats, Building material – flats</td>
<td>Bronchial ca.</td>
</tr>
<tr>
<td>Rtg radiation, radium</td>
<td>Radiologists</td>
<td>Skin ca, leukemia</td>
</tr>
<tr>
<td>Radium</td>
<td>Production and application of luminescent dyes</td>
<td>Bone, leukemia</td>
</tr>
<tr>
<td>Radionuclides</td>
<td>Results of accidents of nuclear powerhouse</td>
<td>Thyroidal ca.</td>
</tr>
<tr>
<td>Nuclear explosion</td>
<td>Nuclear weapons, nuclear powerhouse</td>
<td>Leukemia, skin ca</td>
</tr>
<tr>
<td>UV radiation</td>
<td>Farmers, sailors etc.</td>
<td>Skin ca</td>
</tr>
</tbody>
</table>
### CARCINOGENIC FACTORS IN WORKINGPLACE

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>ENVIRONMENT</th>
<th>LOCALISATION OF TUMOR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons in soots, tar and oils</td>
<td>Chimneysweeper; gasworks workers; asphalters etc.</td>
<td>Scrotum, skin, bronchus</td>
</tr>
<tr>
<td>2-naftylamine; 1-naftylamine</td>
<td>Chemists; rubbers workers; gasworks workers; smokers</td>
<td>Urinary bladder</td>
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<tr>
<td>Benzidine; 4-aminobiphenyl</td>
<td>Chemists</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>FACTOR</td>
<td>ENVIRONMENT</td>
<td>LOCALISATION OF TUMOR</td>
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<tr>
<td>Asbestos</td>
<td>Workers with asbestos docks and isolateurs</td>
<td>Bronchus, pleura, peritoneum</td>
</tr>
<tr>
<td>Arsenic (As₂O₃)</td>
<td>Tanners and processing of wool; Miners in gold mine; Workers in vineyard (spraying); Smelters of ores</td>
<td>Skin, bronchus and liver</td>
</tr>
<tr>
<td>Bis-(chloromethyl)-ether</td>
<td>Manufacturing of ionexchanger</td>
<td>Bronchus</td>
</tr>
<tr>
<td>Benzene</td>
<td>Workers with adhesives, painters, laboratories (histol.)</td>
<td>Bone marrow (leukemia)</td>
</tr>
<tr>
<td>Nitrogen yperite (mustard gas) - trichlorotriethylamine</td>
<td>Manufacturing of poisonous gases</td>
<td>Bronchus, Larynx, Nasal sinuses</td>
</tr>
<tr>
<td>Vinylchlorid</td>
<td>Manufacturing of PVC</td>
<td>Liver (angiosarkomas)</td>
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<tr>
<td>LOCALISATION OF TUMOR</td>
<td>TUMOR TYPE</td>
<td>AGENTS</td>
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<tr>
<td>Skin</td>
<td>Epidermoidal carcinoma and basalioma</td>
<td>Arsenic (As₂O₃) Coal tar Ionization radiation Sun radiation</td>
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<tr>
<td>Lungs</td>
<td>Bronchogenic carcinoma</td>
<td>Asbestos Ionization radiation</td>
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<tr>
<td>Bone marrow</td>
<td>Leukemia</td>
<td>Benzene Ionization radiation</td>
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<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Squamocellular carcinoma</td>
<td>Aromatic amine</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteogenic sarcoma</td>
<td>Ionization radiation</td>
</tr>
</tbody>
</table>
Tabacco N-nitrosamines

- Chewing of tobacco is associated with carcinoma of oral cavity
- In oral squamous cell carcinomas leads to mutation in p53 gene

Examples:
  - transversion: TGT → TGG
  - insertion: CTG → CTTG
Natural carcinogens

Some mykotoxins, frequently Aflatoxins

• Molecule produced by mould Aspergillus flavus → mycotoxin Aflatoxin
• Discovered in mouldy foods → groundnut (groundnut flour)
• Cause mutation in DNA – cause transverse G→T in p53 molecule in position 249 in serine
• Relationship to hepatocellular carcinoma in south-eastern Asia and south Africa
• HBV is synergic factor for carcinogenesis with aflatoxin B₁
• Whole foodstuff imported from tropics and fodder plants by could be tested on mycotoxins
Tumor viruses

substantially contributed to understanding
of tumor transformation mechanisms.

• RNA viruses – retroviruses → tumors by animals and people
  a) rapidly transforming → in genome have oncogen – v-onc
  b) slowly transforming → in genome have not oncogene
  c) transregulating → HTLV I/II – humen

• DNA viruses → inactivation of tumor suppressor genes
  – Human Papilloma Viruses from PAPOVA virus group →
    induce cervix ca and others. The E6 and E7 oncoproteins of the high-risk HPVs interfere with
    the functions of negative cellular regulators, including the tumor-suppressor proteins p53 and
    pRB, respectively.
  – Adenoviruses → exp. tumors in rodents
  – Human herpes viruses (some) – EBV, HHV8
Viruses associated with human tumors

- **DNA viruses**
  - *Human papilloma viruses* (HPV) from papovaviruses
  - *Herpesviruses*
    - Epstein-Barr virus (EBV, HHV-4) – associated with infectious mononucleosis (IM), Burkitt’s lymphoma (BL), nasopharyngeal carcinoma (NPC), Hodgkin’s lymphoma (HD) and T-cell lymphoma
    - Human herpesvirus 8 (HHV-8) [KSHV] – 1994
  - *Hepatitis B virus* (HBV) – possibly direct precipitation in primary hepatoma by genomic integration and effect of the viral protein X

- **RNA viruses - retroviruses**
  - HTLV-I/II (Human T-lymphotropic viruses I a II)
  - HIV – can cause as cofactor of protooncogen activation
**Oncogenes**

- **Proto-oncogen** = counterpart of *viral oncogene*
  - normal cellular genes coding protein participating in control of cellular growth and differentiation after action of external stimulus.
  - permanent activation by mutation $\rightarrow$ change on oncogenes
  - 3 letter abbreviation

- **Oncogenes** - genes coding proteins essential for initiation, promotion and development of malignant state

- $>$100 of different oncogenes
- Discovery of transforming genes – *v-onc* – in genome of oncoretroviruses contributed to discovery of cellular protooncogenes, resp. oncogenes
## Overview of Genes Associated with Tumors

<table>
<thead>
<tr>
<th>Class of Oncogenes</th>
<th>Oncogene</th>
<th>Retrovirus</th>
<th>Nonviral Tumor</th>
<th>Normal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I: Growth Factors</strong></td>
<td>sis</td>
<td>Simian sarcoma v.</td>
<td></td>
<td>Platelet growth factor</td>
</tr>
<tr>
<td><strong>Class II A: Membrane Receptors R.F.</strong></td>
<td>erb B1</td>
<td>Avian erythroblastosis v.</td>
<td>Neuroblastoma</td>
<td>Epidermal growth factor</td>
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<tr>
<td></td>
<td>erb B2</td>
<td></td>
<td></td>
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<tr>
<td><strong>Class II B: Intracellular Receptors</strong></td>
<td>erb A</td>
<td>avian erythroblastosis v.</td>
<td></td>
<td>Thyroidal hormone receptor</td>
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<tr>
<td><strong>Class III A: (tyrosine-kinases) Intracellular Signal Transductor</strong></td>
<td>src</td>
<td>Rous sarcoma v.</td>
<td>Sarcoma, Chron. myeloid leukemia</td>
<td>Tyrosinkinase</td>
</tr>
<tr>
<td></td>
<td>abl</td>
<td>Abelson sarcoma v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class III B: (ser/thr-kinases) Intracellular Signal Transductor</strong></td>
<td>mos</td>
<td>Moloney leukemia v.</td>
<td>Ser/thr-kinase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raf</td>
<td>Mouse sarcoma virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class III C: (G-proteins) Intracellular Signal Transductors</strong></td>
<td>H-ras</td>
<td>Harvey rat v.</td>
<td>Urinary bladder ca., Mammary ca., Skin ca. and others</td>
<td>GTP-bonding protein</td>
</tr>
<tr>
<td></td>
<td>K-ras</td>
<td>Kirsten rat v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N-ras</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Class IV: Nuclear Transcription Factors</strong></td>
<td>myb</td>
<td>Avian myeloblastosis v.</td>
<td>Transcription regulation</td>
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<tr>
<td></td>
<td>myc</td>
<td>Avian MC29 v.</td>
<td></td>
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<tr>
<td></td>
<td>jun</td>
<td>Avian sarcoma v.</td>
<td></td>
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<tr>
<td></td>
<td>fos</td>
<td>FBJ sarcoma v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class V: Antiapoptotic Factors</strong></td>
<td>Bcl2</td>
<td>B-cell lymphoma</td>
<td>Bax inactivation</td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms of proto-onkogene activation

1. Mutation

* Point mutation/deletion/insertion - in human tumors most often provided mutation Ras
* It causes a constitutive (permanent) activation of Ras protein function

2. Amplification of gene → very much gene copy

* follow from repeated unscheduled synthesis of DNA (repair) during growth cycle of single cells

Amplification type

Double minutes (very small fragments of chromosomes)

HSR – Homogeneous Staining Region – long regions of repeated genes in chromosomes

HER2/neu/c-erbB2 by breast ca.; N-myc - neuroblastoma
Mechanisms of proto-onkogene activation

3. Shortening (deletion) = truncation
   – Gene is partially missing → resulting protein is truncated and constantly active

   **Example**: in EGF receptor is absent domain binding a ligand and receptor is continually active → glioblastoma multiforme
4. Chromosomal conversions

* chromosomal translocation; inversion

- **Gene activation** - transcription activation of proto-oncogenes
  
  e.g. follicular lymphoma - t(14:18) - Bcl2
  
  Burkitt’s lymphoma - t(8:14) - c-myc

- **Gene fusion**: coding of chimer (fusion) protein
  
  e.g. CML t(9:22) - BCR/Abl
  
  APML t(15:17) - PML/Rar
Tumor suppressor genes - antioncogenes

- Genes, which control a cellular division
- Repair genes of DNA
- Cellular „suicidal“ genes
- Recessive genotype → loss of heterozygozity (LOH)
- Control a cellular proliferation
  - >20 tumor suppressor genes
  - Hereditary tumors: colon ca., retinoblastoma, Wilms‘s tumor of kidney, breast ca., neurofibromatosis, Li-Fraumeni syndroma, xeroderma pigmentosum
Repair genes of DNA

Excise nucleotide repair
  * Xeroderma pigmentosum

Mismatch repair
  *) Hereditary Non-Polyposis Colorectal Cancer (HNPPCC)
FOR FORMATION OF MALIGNANT TUMOR, EFFECT OF ONLY ONE FACTOR IS INSUFICIENT, BUT STRIKES MUST BE MORE AND IN SEVERAL POSITIONS!
STAGE OF CARCINOGENESIS

APC = Adenomatous Polyposis Colon  
DCC = Deleted in Colon Cancer  
MCC = Mutated in Colon Cancer  
ASCUS = Atypical Squamous Cells of Undetermined Significance  
LGSIL = Low-Grade Squamous Intraepithelial Lesion  
HGSIL = High-Grade Squamous Intraepithelial Lesion
Can we optimize the selection of current therapies? 
Is anatomy the best way to choose therapy?

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>% of Men</th>
<th>Number of Cases</th>
<th>% of Women</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>31%</td>
<td>285,900</td>
<td>25%</td>
<td>270,600</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
<td></td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>10%</td>
<td></td>
<td>11%</td>
<td></td>
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<tr>
<td>Pancreas</td>
<td>5%</td>
<td></td>
<td>6%</td>
<td></td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
<td>5%</td>
<td></td>
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<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
<td>4%</td>
<td></td>
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<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Liver/intrahepatic bile duct</td>
<td>3%</td>
<td></td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td></td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td></td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>22%</td>
<td></td>
<td>23%</td>
<td></td>
</tr>
</tbody>
</table>

- Lung & bronchus: 285,900 cases (25% of women)
- Breast: 15% of women
- Colon & rectum: 11% of women
- Pancreas: 6% of women
- Ovary: 5% of women
- Non-Hodgkin lymphoma: 4% of women
- Leukemia: 4% of women
- Esophagus: 4% of women
- Liver/intrahepatic bile duct: 3% of women
- Urinary bladder: 3% of women
- Kidney: 3% of women
- All other sites: 23% of women