Molecular Biology of Human Cancers

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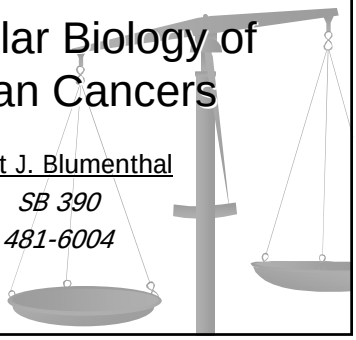
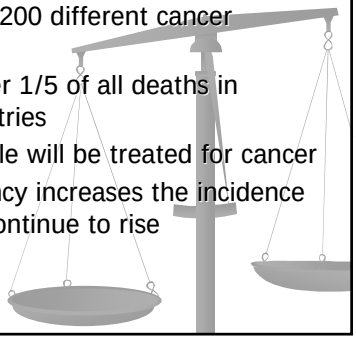


Introduction to Human Cancers

- There are over 200 different cancer "diseases"
- Account for over 1/5 of all deaths in Industrial Countries
- 1 out of 3 people will be treated for cancer
- As life expectancy increases the incidence of cancer will continue to rise

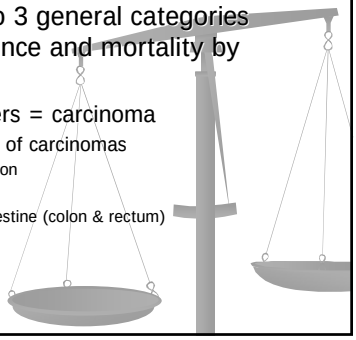


Definitions

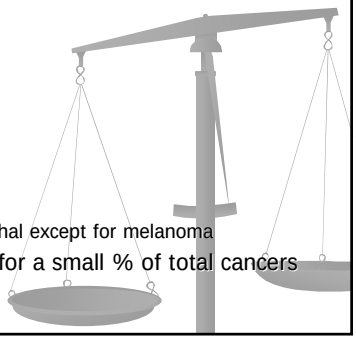
Table 1.1. *Some basic definitions in oncology*

Designation	*Meaning*	*Remarks*
Tumor	any abnormal increase in the size of a tissue	also used for swellings, unusual for benign hypertrophy or hyperplasia
Malignant tumor	a tumor characterized by permanently increased cell proliferation, progressive growth, and invasion or metastasis	corresponding to 'cancer' in everyday language
Benign tumor	a tumor lacking growth beyond a circumscribed region within a tissue	
Cancer	a malignant tumor	preferentially used for (suspected or verified) systemic disease
Neoplasia	a malignant tumor	
Leukemia	a malignant tumor formed by cells of the hematopoetic cells and found in the blood	
Lymphoma	a malignant tumor formed by cells of the lymphocyte cell lineage	can be restricted to specific lymphoid organs
Sarcoma	a solid malignant tumor formed from connective tissue (mesenchymal) cells	
Carcinoma	a solid malignant tumor formed from cells of epithelial origin	
Adenoma	a benign tumor displaying a glandular structure	often originated from gland tissue
Adenocarcinoma	a malignant tumor showing resemblance to glandular structures	often originated from gland tissue
Tumor stage	a measure of the physical extension of a (malignant) tumor	different systems are in use, for different (and even the same) cancer types
Tumor grade	a measure of the cellular and/or architectural atypia of a tumor	different systems are in use, for different (and even the same) cancer types

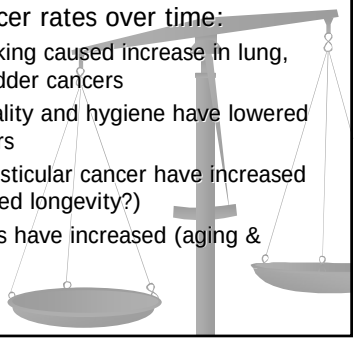
- Cancers fall into 3 general categories based on incidence and mortality by organ:
  - Epithelial cancers = carcinoma
    - Most prevalent of carcinomas
      - 4 most common
        - Lung
        - Large intestine (colon & rectum)
        - Breast
        - Prostate



- Other Carcinomas arise in the :
  - Bladder
  - Stomach
  - Liver
  - Kidney
  - Pancreas
  - Esophagus
  - Cervix
  - Ovary
  - Skin- rarely lethal except for melanoma
- Each accounts for a small % of total cancers



- Changes in cancer rates over time:
  - Increased smoking caused increase in lung, kidney and bladder cancers
  - Better food quality and hygiene have lowered stomach cancers
  - Prostate and testicular cancer have increased (due to increased longevity?)
  - Melanoma rates have increased (aging & lifestyle?)



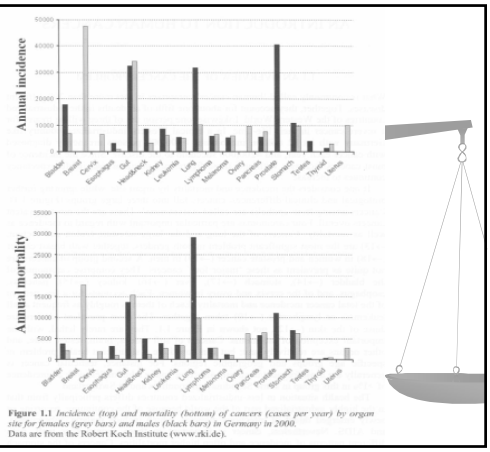


Figure 1.1 *Incidence (top) and mortality (bottom) of cancers (cases per year) by organ site for females (grey bars) and males (black bars) in Germany in 2000.* Data are from the Robert Koch Institute (www.rki.de).

- Must understand the underlying causes of geographical differences in cancer incidence
  - This can lead to increased prevention (rates of prostate cancer 20X less in Asian residents than in relatives who grew up in USA)

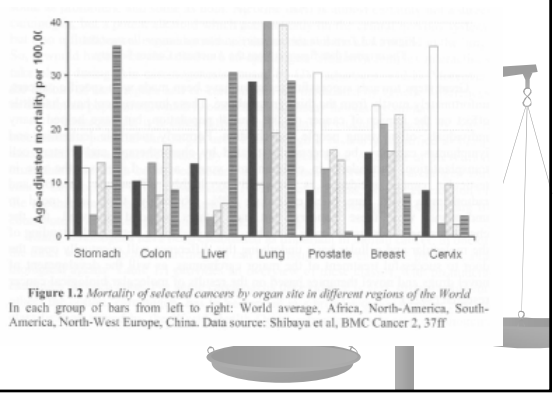


Figure 1.2 *Mortality of selected cancers by organ site in different regions of the World* In each group of bars from left to right: World average, Africa, North-America, South-America, North-West Europe, China. Data source: Shibaya et al, BMC Cancer 2, 37ff

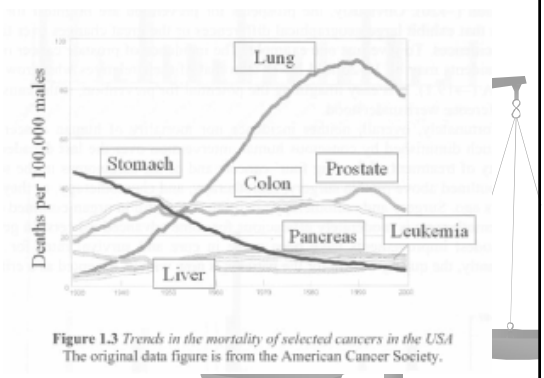


Figure 1.3 *Trends in the mortality of selected cancers in the USA*
The original data figure is from the American Cancer Society.

- Treatment protocols have done little to lessen incidence of cancers:
  - Surgery
  - Radiotherapy
  - Chemotherapy
- The QUALITY of life rather than a CURE is the ultimate goal
- So many different types of cancers there will be no one "cure" or treatment
- Understanding mechanism will lead to potential cure/treatment

Causes of Cancer

- Exogenous chemical, physical and biological carcinogens
  - Humans vary in ability to cope with each different inducer
    - Genetics
    - Stress
    - Level of exposure
- Endogenous causes
  - Chronic inflammation
  - Metabolic intermediates (O_2- intermediates)
  - DNA replication and repair

- Tumor Initiators vs Tumor Promotors vs Whole Carcinogen
  - Initiators- cause minimum of two genetic mutations
  - Promotors- are not mutagenic themselves and do not cause cancer, but stabilize mutations by inducing cell replication
  - Whole carcinogen- has both properties (can induce and promote

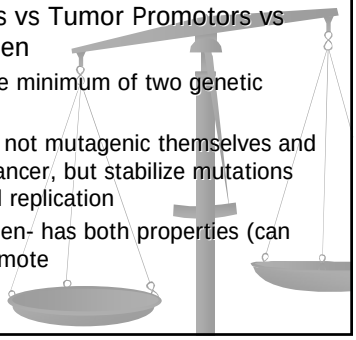
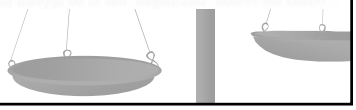
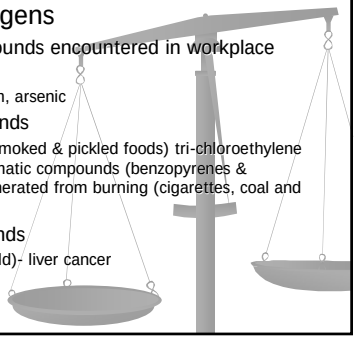


Table 1.1. *Types and examples of human carcinogens*

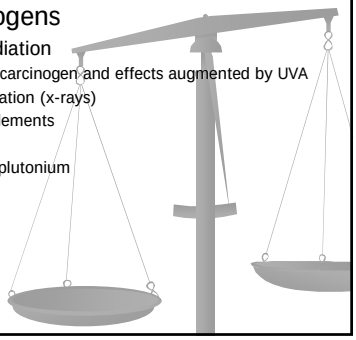
Type of carcinogen	*Examples*
Chemical carcinogens	Nickel, cadmium, arsenic, nitrosamines, trichloroethylene, arylamines, benzopyrene, aflatoxins, reactive oxygen species
Physical carcinogens	UV irradiation (specifically UVB), ionizing radiation
Biological carcinogens	Human papilloma virus (e.g. strain 16), Epstein-Barr-Virus, Hepatitis virus B, Helicobacter pylori, *Schistosoma mansoni*
Endogenous processes	DNA replication, metabolic reactions generating reactive oxygen species, chronic inflammation



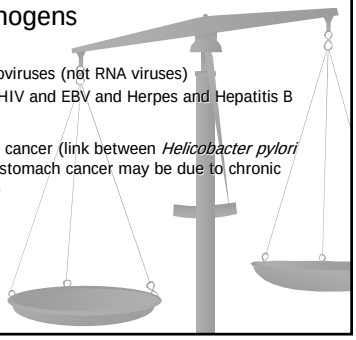
- Chemical carcinogens
  - Inorganic compounds encountered in workplace environments
    - Nickel, cadmium, arsenic
  - Organic compounds
    - Nitrosamines (smoked & pickled foods) tri-chloroethylene (cleaning), aromatic compounds (benzopyrenes & arylamines) generated from burning (cigarettes, coal and fuel)
  - Natural compounds
    - Aflatoxin A (mold)- liver cancer
    - Hormones
    - Medical drugs



- Physical Carcinogens
  - Energy rich radiation
    - UVB is a skin carcinogen and effects augmented by UVA
    - Gamma irradiation (x-rays)
    - Radioactive elements
      - Radon
      - Uranium/plutonium
      - Iodine



- Biological Carcinogens
  - Viruses
    - DNA and retroviruses (not RNA viruses)
      - HPV and HIV and EBV and Herpes and Hepatitis B
  - Bacteria
    - Rare to cause cancer (link between *Helicobacter pylori* infection and stomach cancer may be due to chronic inflammation)



- Endogenous Carcinogens
  - Involved in cancer development through modulation of the response to exogenous carcinogens
  - Also through strictly endogenous pathways:
    - Normal metabolism- generation of nitrosamines, aromatic amines, reactive aldehydes and reactive O_2 species
      - Level of these dependent upon diet, exercise
    - DNA repair mechanisms- damage all the time- repair effected by age or cells removed by apoptosis- if the mechanisms affected then cancer may arise
    - Recognition by immune response (immune surveillance)
    - Chronic infection (replication of cells [liver])

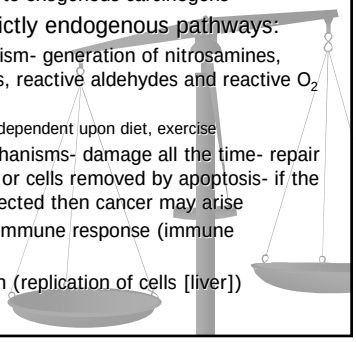
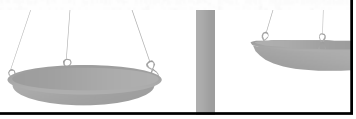


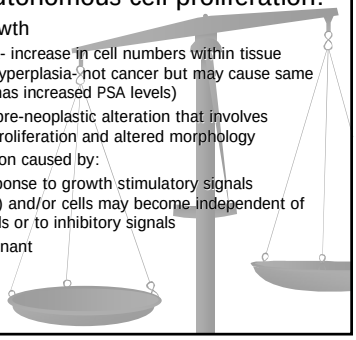
Table 1.3. *Characteristic properties of human cancers*

Property
Increased cell proliferation (often autonomous)
Insufficient apoptosis
Altered cell and tissue differentiation
Altered metabolism
Genomic instability
Immortalization (growth beyond replicative senescence)
Invasion into different tissue layers and other tissues (with disturbed tissue architecture)
Metastasis into local lymph nodes and distant tissues

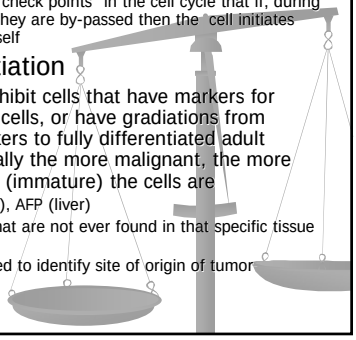


Properties of Cancer Cells

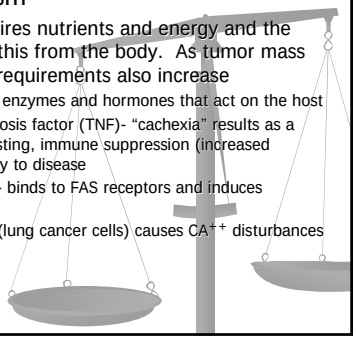
- Increased and autonomous cell proliferation:
  - Unregulated growth
    - Hyperplasia- increase in cell numbers within tissue (prostatic hyperplasia- not cancer but may cause same problems- has increased PSA levels)
    - Dysplasia- pre-neoplastic alteration that involves increased proliferation and altered morphology
  - Hyperproliferation caused by:
    - Altered response to growth stimulatory signals (receptors?) and/or cells may become independent of these signals or to inhibitory signals
  - Benign vs malignant



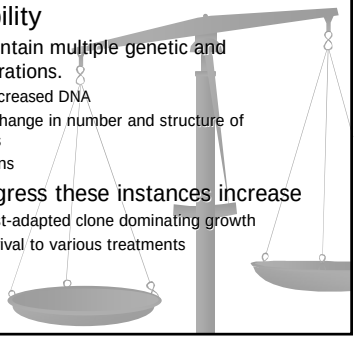
- Insufficient Apoptosis
  - "programmed cell death"
    - There are "check points" in the cell cycle that if, during the cycle, they are by-passed then the cell initiates death of itself
- Altered Differentiation
  - Cancers may exhibit cells that have markers for "mature" tissue cells, or have gradiations from embryonic markers to fully differentiated adult markers- generally the more malignant, the more undifferentiated (immature) the cells are
    - CEA (colon), AFP (liver)
    - Antigens that are not ever found in that specific tissue type
    - May be used to identify site of origin of tumor



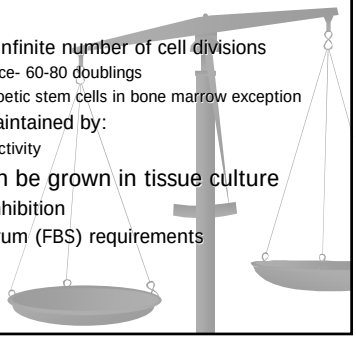
- Altered Metabolism
  - Cell growth requires nutrients and energy and the cancer cells get this from the body. As tumor mass increases these requirements also increase
    - Tumors release enzymes and hormones that act on the host
      - Tumor necrosis factor (TNF)- "cachexia" results as a general wasting, immune suppression (increased susceptibility to disease
      - FAS Ligand- binds to FAS receptors and induces apoptosis
      - Calcitonin- (lung cancer cells) causes CA^{++} disturbances



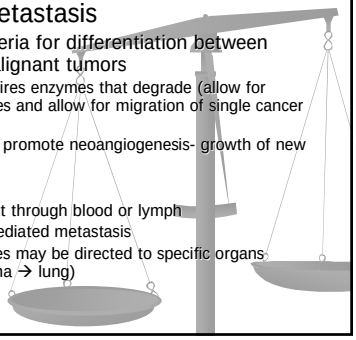
- Genomic Instability
  - Cancer cells contain multiple genetic and epigenetic alterations.
    - Polyploidy- increased DNA
    - Aneuploidy- change in number and structure of chromosomes
    - Point mutations
  - As cancers progress these instances increase
    - Results in best-adapted clone dominating growth
    - Selective survival to various treatments



- Immortalization
  - Capable of an infinite number of cell divisions
    - Cell senescence- 60-80 doublings
      - Hematopoetic stem cells in bone marrow exception
  - Immortality maintained by:
    - Telomerase activity
  - Cancer cells can be grown in tissue culture
    - Lack contact inhibition
    - Have lower serum (FBS) requirements

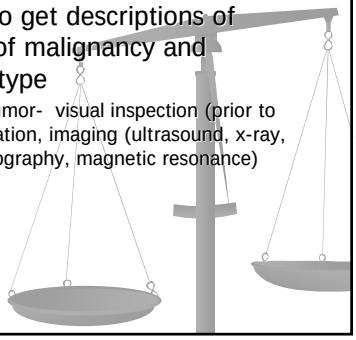


- Invasion and Metastasis
  - Invasion is criteria for differentiation between benign and malignant tumors
    - Invasion requires enzymes that degrade (allow for escape) tissues and allow for migration of single cancer cells
    - Enzymes that promote neoangiogenesis- growth of new blood vessels
  - Metastasis-
    - Movement through blood or lymph
    - Biopsy mediated metastasis
    - Metastases may be directed to specific organs (melanoma → lung)



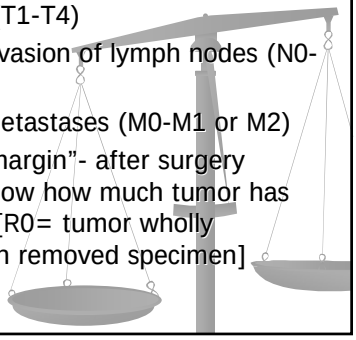
Classification of Tumors

- Staging: need to get descriptions of tumor, degree of malignancy and histological subtype
  - Extension of tumor- visual inspection (prior to surgery)- palpation, imaging (ultrasound, x-ray, computer tomography, magnetic resonance)



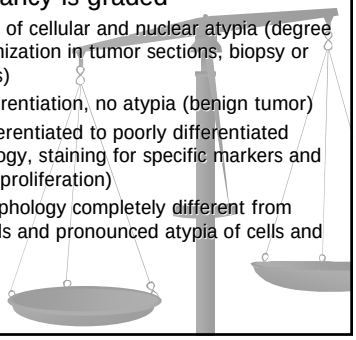
TNM Staging System

- T= tumor size (T1-T4)
- N= extent of invasion of lymph nodes (N0-N1 or N2)
- M= extent of metastases (M0-M1 or M2)
- R= “resection margin”- after surgery necessary to know how much tumor has been removed [R0= tumor wholly contained within removed specimen]



Grading

- Degree of malignancy is graded
  - Score the degree of cellular and nuclear atypia (degree of tissue disorganization in tumor sections, biopsy or single tumor cells)
  - G0= normal differentiation, no atypia (benign tumor)
  - G1-G3= well differentiated to poorly differentiated (look at morphology, staining for specific markers and look at extent of proliferation)
  - G4= cellular morphology completely different from normal tissue cells and pronounced atypia of cells and nuclei



Treatment of Cancer

- Surgery- for localized cancer
- Irradiation- for localized cancer and fast growing cancers
- Drugs-
  - leukemia, lymphoma, metastatic cancers (stop DNA replication, transcription, replication)- *how to target just tumor cells???*
  - Receptor targeting
  - Hormone and anti-hormone therapy
  - Stimulation of immune response (CSF's & IL's)
- Combination Therapy
  - Adjuvant Therapy- surgery followed by Chemo-
  - Neo-Adjuvant Therapy- chemo- prior to surgery to shrink tumor