Neoplasm – mass of tissue that grows excessively even if you remove starting stimulus

Benign tumours are well differentiated (look similar to tissue of origin) while malignant tumours are poorly differentiated

If the tumour is metastatic, it is malignant

Benign tumours (usually end with –oma)

- Adenoma – glandular cells
- Leiomyoma – smooth muscle cells
- Chondroma – chondrocytes
- Papilloma – finger-like projections
- Polyp – projects upward, forming a lump
- Cystadema – has hollow space (cyst) inside

Most benign tumours have a fibrous capsule

Malignant tumours

- Carcinomas – epithelial tissue
    - Adenocarcinoma – glandular cells
    - Squamous cell carcinoma – squamous cells
- Sarcomas – mesenchymal tissue
    - Chondrosacroma – chondrocytes
    - Angiosarcoma – blood vessels
    - Rhabdomyosarcoma – skeletal muscle cells

Mixed tumours – show divergent differentiation (not to be confused with teratomas)

- Pleomorphic adenoma – glands + fibromyxoid stroma
- Fibroadenoma – glands + fibrous tissue

Confusing Terms

- Lymphoma, mesothelioma, melanoma, seminoma

Non-tumours

- Hamaratoma – mass of disorganized indigenous tissue
- Choristoma – heterotopic rest of cells

Names that seem to come out of nowhere

- Nevus
- Leukemia
- Hydatidiform mole

Tissue of origin	Benign	Malignant
Fibrous tissue	Fibroma	Fibrosarcoma
Fat	Lipoma	Liposarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteogenic sarcoma
Blood vessels	Hemangioma	Angiosarcoma
Mesothelium		Mesothelioma
Hematopoietic cells		Leukemia
Lymphoid cells		Lymphoma
Squamous epithelium	Squamous cell papilloma	Squamous cell carcinoma
Glandular epithelium	Adenoma	Adenocarcinoma
	Papilloma	Papillary adenocarcinoma
	Cystadenoma	Cystadenocarcinoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Melanocytes	Nevus	Melanoma

Anaplasia – cells resembling stem cells (poorly differentiated)

- Well differentiated – closely resembles tissue of origin
- Well differentiated tumours are usually benign

Anaplasia – cell do NOT de-differentiate (misnomer) – almost always indicates malignancy

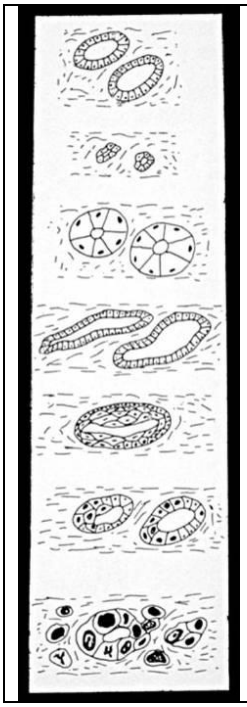
- Pleomorphism
- Hyperchromatic, large nuclei
- Bizarre nuclear shapes, distinct nucleoli
- Lots of mitosis, atypical mitosis
- Architectural anarchy

Dysplasia – disorderly growth

- Pleomorphic, hyperchromatic, large nuclei, lots of mitosis, architectural anarchy
    - Different in that it does NOT have bizarre nuclear shapes/distinct nucleoli
- Describe disorderly changes in non-neoplastic **epithelial** cells
- Graded as mild, moderate, severe
    - Mild and moderate are reversible
    - Severe usually progresses to carcinoma in situ (CIS)
        - Next step is an invasive carcinoma

- Differentiation – only neoplastic (abnormal differentiation of) cells, can apply to any cell type
- Dysplasia – only non-neoplastic cells, on applies to epithelial cells

- Non-neoplastic epithelial cells
    - Mild dysplasia → moderate dysplasia → severe dysplasia → → → carcinoma in situ
- Neoplastic cells
    - Well differentiated → moderately differentiated → poorly differentiated → anaplastic



Normal

Atrophic

Hypertrophic

Hyperplasia

Metaplasia

Dysplasia

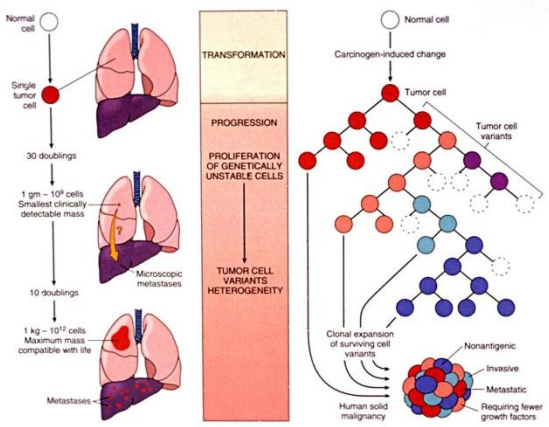
Invasive carcinoma

Malignant tumors (poorly differentiated) grow faster than benign (well differentiated) ones. Growth is dependent on:

- Blood supply
- Hormonal factors
- Emergence of aggressive sub-clones

Growth fraction = cells that are actively dividing

- Early (subclinical) – high GF
- Later (clinical) – low GF



Type of tumour

- Leukemia, lymphoma, small cell lung cancer – high GF
- Breast, colon cancer – low GF

Treatment

- High GF tumor – chemotherapy/radiation
- Low GF tumor – treat by debulking

Most tumours require at least 30 doublings (1million cells) to be detectable. They have usually already learned to metastasize by then.

Malignant tumours – infiltrate, invade, destroy surrounding tissues. Metastasize to other sites. Not encapsulated

- Carcinoma in situ – malignant tumour not yet broke out of its localized area
    - Invasive carcinoma – started to branch out of its localized area
    - Metastasizing carcinoma – colonized other areas

Metastasis – development of secondary tumor implants in distant tissue

- Dependent on
    - Type of tumor
    - Size of tumor
    - Degree of differentiation of tumour
- Half of all diagnoses with malignancies have metastases at time of diagnosis

3 ways of metastasis

- Seeding
    - Tumor invades body cavity
    - Bits break off at implant on peritoneal cavity
    - Ovarian cancer
- Lymphatic drainage
    - Tumor spreads to local lymph nodes
        - Sentinel lymph node (first node to receive lymph drainage) first
    - Moves through thoracic duct
    - Empties into subclavian vein
    - Carcinomas like to spread this way
- Hematogenous spread
    - Veins are easier to invade than arteries
    - Liver and lungs are most common metastatic destinations
    - Some tumors like other sites better
        - Prostate → bone
        - Lung cancers → adrenals, brain
    - Sarcomas like to spread this way (so do carcinomas)

- 1.4M cases of new cancer last year
- 565K deaths last year
    - 2nd leading cause of death (after heart disease)
- Most common forms
    - Men – prostrate
    - Women – breast
- Deadliest cancer – lung (for both genders)
- Decreased death rates for
    - Cervical cancer – pap smears
    - Colon cancer – earlier detection
    - Breast cancer – earlier detection
    - Lung cancer in men – less smokers
    - Some types of leukemia – new treatments
- Increased death rates for
    - Lung cancer in women – more smokers

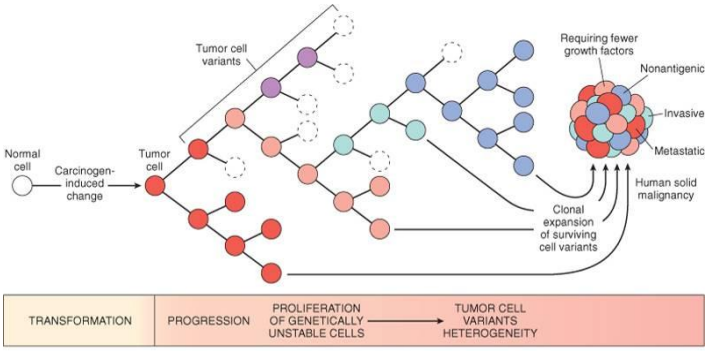
- Environmental factors
    - Breast cancer rate in USA 5x more than Japan
    - Stomach cancer rate in Japan 7x more than USA
    - Liver cancer NOT frequent in USA, frequent in Africa
    - These probably due to environmental (not hereditary) factors
    - Most sporadic cancers caused by environmental factors
        - Sunlight – skin cancer
        - Smoke – lung cancer
        - Alcohol – liver, breast cancers
        - HPV – cervical cancer

Asbestos	roofing, tiles	mesothelioma
Benzene	light oil, solvents	leukemia
Beryllium	missile fuel	lung cancer
Ethylene oxide	ripening agents, fumigants	leukemia
Radon	uranium decay, mines	lung cancer
Vinyl chloride	refrigerants	angiosarcoma and liver cancer
Nickel	welding, ceramics	nose and liver cancers
Cadmium	batteries	prostate cancer

- Age
    - Elderly – most cancers occur between 55-75
    - Children – 10% of all kid deaths, leukemia/lymphoma, CNS tumors, sarcoma
- Heredity
    - Inherited cancer syndromes
        - Dominance
        - Retinoblastoma (Rb)
        - Familial polyposis coli
    - Familial cancers
        - Most common sporadic cancers have familial forms too
        - Breast, colon, ovary, brain
        - Occur earlier, are often deadlier
    - Syndromes of defective DNA repair
        - Recessive
        - Xeroderma pigmentosum
- Acquired preneoplastic syndromes
    - Persistent regenerative cell replication
        - Chronic skin fistula – squamous cell carcinoma
        - Cirrhosis – liver cancer
    - Hyperplastic and dysplastic proliferations
        - Atypical endometrial hyperplasia – endometrial cancer
        - Dysplastic bronchial mucosa – lung cancer
    - Chronic atrophic gastritis – stomach cancer
    - Chronic ulcerative colitis – colon cancer
    - Leukoplakia – squamous cell carcinoma

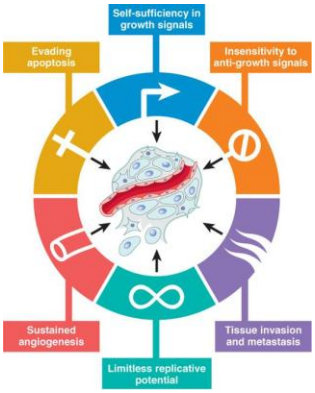
Causes of non-lethal genetic damage (4 genes)

- Proto-oncogenes – genes that promote growth
- Tumor suppressors – genes that inhibit growth
- Genes that regulate apoptosis
- Genes that repair DNA



Cancer progresses in multiple steps

Cancer genes cause bad things in cells

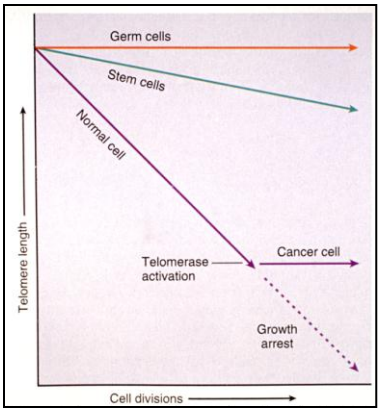


- Autonomous growth, insensitivity to inhibition factors, evasion of apoptosis, limitless replication, sustained angiogenesis, invasion and metastasis

- Proto-oncogene – normal gene whose product promotes cell growth
  - Oncogene – mutated proto-oncogene
  - Oncoprotein – product of an oncogene

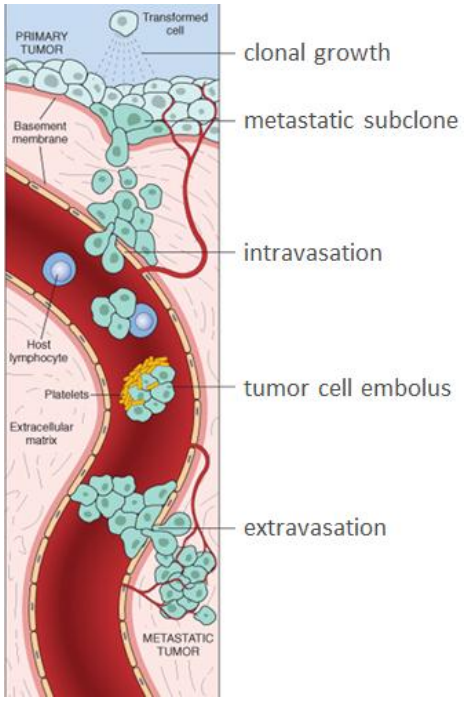
- In normal cells
  - Growth factor binds to receptor
  - Receptor activates signal transducing protein
    - Activates 2ndary messenger
  - 2ndary messenger talks to transcription factors
  - Nuclear transcription factors start DNA transcription
  - Cyclins move the cell through the cell cycle
- In cancer cells
  - Growth factors made by cell itself
  - Receptors may be overexpressed or always on
  - Signal transducing proteins may always be on
  - Nuclear transcription factors may always be expressed
  - Cyclins may be overactive
  - All means the cell has uncontrolled division

- RAS – signal transduction gene (always on in cancer) - dominant
- Tumor suppressor genes
  - RB gene – stops cells at G_1 checkpoint
    - Mutant Rb is inactive – allows cells to bypass checkpoint
    - Patients with 2 mutated genes – increased risk of retinoblastoma, increased risk of other carcinomas
  - P53 gene (genome guardian) – if DNA is damaged, p53 tells Rb to stop cell cycle to allow for repair
    - If repair is not possible, p53 tells cell to undergo apoptosis
    - Most tumors have p53 mutations
- Evasion of apoptosis – if these proteins are mutated, cell becomes immortal
- Limitless replication – normal cell only replicates 60-70x, telomeres get shorter
  - Stem cells use telomerase to maintain telomere length and keep replicating



- Sustained angiogenesis
    - Tumor cells, like all other cells, need blood supply
    - Can't grow more than 1-2cm away from supply vessels
    - Tumor cells eventually learn how to stimulate angiogenesis
    - Lots of cytokines are involves (VEGF)
    - Tumor vessels are abnormal
        - Normal networks – stable, structure and function of wall and network appropriate to location
        - Tumor networks – evolving, unstable, abnormal function inappropriate to location

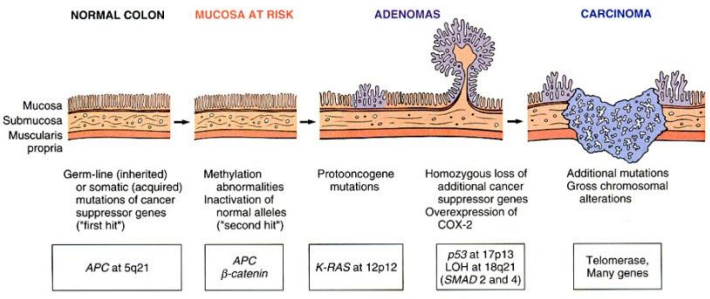
- Invasion and metastasis
    - To invade, tumor cells must
        - Loosen contact between cells
        - Degrade ECM
        - Migrate away from original site (metastasize)
    - Some tumors lodge in nearest capillary bed
    - Some tumors show tropism (preferential site of invasion)



- How genetic mutations arise
    - Constant exposure to mutagenic agents, but corrected because cells are constantly under repair. Inherited defects to those controls increases chance of tumor
        - Cell divisions per day = 10^{11}
        - Spontaneous mutation rate = 10^{-6}
        - Mutations per day = 10^{5}
- Hereditary DNA repair defects
    - Hereditary nonpolyposis colon cancer syndrome
        - Failure of mismatch repair (no spellchecker)
        - Inherited one mutation, acquire the other
        - Familial colon cancers
    - Xeroderma pigmentosum
        - Failure of nucleotide excision repair system
        - Small sun exposure leads to skin cancer

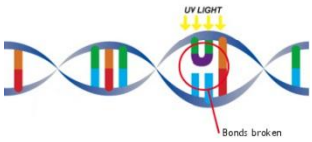
- Steps to cancer
    - Every tumor results from accumulation of lots of mutations (average = 90)
    - Normally, body fixes or rids mutated cells (Rb, p53, etc)
    - For a tumor cell to propagate, mutation must be in one of these guardian/proofing genes

- Chromosomes
    - Genetic damage can be subtle (invisible on karyotype)
    - Or large, visible on karyotype
    - Some karyotype abnormalities occur predictably in certain tumors
        - Leukemias, lymphomas, solid tumors



- Balanced translocations
    - Common!
    - Either place proto-oncogene next to a promoter
    - Or create a fusion gene that makes a bad growth promoting product
    - Most common in hematopoetic tumors (ex:// Ph chromosome)
- Deletions
    - Deletion of part or all of a chromosome
    - Usually deletion of a tumor suppressor gene
    - Most common in solid tumors (ex:// deletion of 13q14 in Rb)

- Agents
    - Chemical
        - Direct-acting agents
            - Carcinogenic as-is
            - Most are chemotherapy drugs
            - Cause secondary malignancies (ex:// leukemia)
        - Indirect acting agents
            - Require conversion to become carcinogenic
                - Hydrocarbons (in tobacco, charred meat)
                - Aflatoxin B (from aspergillus infected grains, nuts)
                - Nitrites (food preservative)
        - Mechanisms
            - Highly reactive electrophile groups bind to DNA
            - Important targets = RAS and p53
    - Radiation
        - Ionizing radiation – causes chromosome breakage, translocations
            - Unprotected miners (lung cancer)
            - Atomic bomb survivors (leukemia, other cancers)
            - Therapeutic head/neck radiation (thyroid cancer)
        - UV light – causes formation of pyrimidine dimers
            - Repair pathways usually fix – but can become overwhelmed
            - Ex:// squamous cell carcinoma, melanoma



    - Bugs
        - HTLV-1 – T-cell lymphoma
        - HPV – cervical cancer
        - EBV – various lymphomas
        - HBV and HCV – hepatocellularcarcinoma
        - H. pylori – gastric cancer, lymphoma

Grading and staging (used for malignant tumors, useful for determining treatment and prognosis)

- Grading (somewhat useful)
  - Tells you how nasty tumor looks
  - Pathologic evaluation of tumor (use microscope)
  - Mitosis, pleomorphism, necrosis, other variables
- Staging (very useful)
  - Tells you how far tumor has spread
  - Clinical evaluations of patient (imaging, surgery)
  - TNM system

Grading system for breast cancer

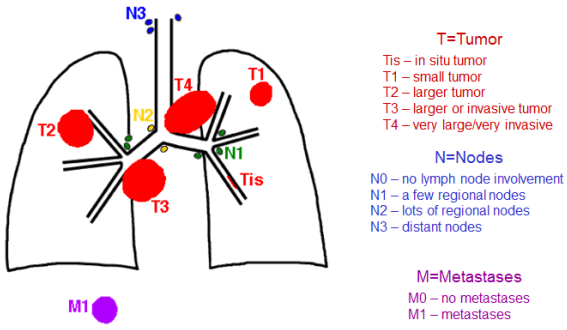
Tubules		Pleomorphism		Mitoses	
lots of tubules	1	small, uniform cells	1	0-9 mitoses/10 hpf	1
some tubules	2	larger, less uniform cells	2	10-19 mitoses/10 hpf	2
rare tubules	3	markedly pleomorphic cells	3	≥20 mitoses/10 hpf	3

add all points together

Grade	Score	5y survival
Low grade	3-5	>95%
Intermediate grade	6-7	80%
High grade	8-9	60%

- Grading – microscopic
- Staging – clinical
- Staging is more useful

TNM staging system for non-small cell lung cancer



TNM staging system for non-small cell lung cancer

Overall stage	T	N	M	Treatment	5y prognosis
Stage 0	Tis	N0	M0	Surgery only	75%
Stage I	T1 or T2	N0	M0	Surgery ± radiation	50%
Stage II	T1	N1	M0	Surgery and radiation ± chemotherapy	30%
	T2	N1	M0		
	T3	N0	M0		
Stage III	T1 or T2	N2	M0	Chemotherapy ± radiation to debulk Maybe surgery	10%
	T3	N1 or N2	M0		
	Any T	N3	M0		
	T4	Any N	M0		
Stage IV	Any T	Any N	M1	Palliative care Maybe chemo or radiation	<2%