ECE 370
Introduction to Biomedical Engineering

Cancer

Leading causes of death in the USA

US Mortality, 2003

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	685,089	28.0
2.	**Cancer**	**556,902**	**22.7**
3.	Cerebrovascular diseases	157,689	6.4
4.	Chronic lower respiratory diseases	126,382	5.2
5.	Accidents (Unintentional injuries)	109,277	4.5
6.	Diabetes mellitus	74,219	3.0
7.	Influenza and pneumonia	65,163	2.7
8.	Alzheimer disease	63,457	2.6
1.	Nephritis	42,453	1.7
10.	Septicemia	34,069	1.4

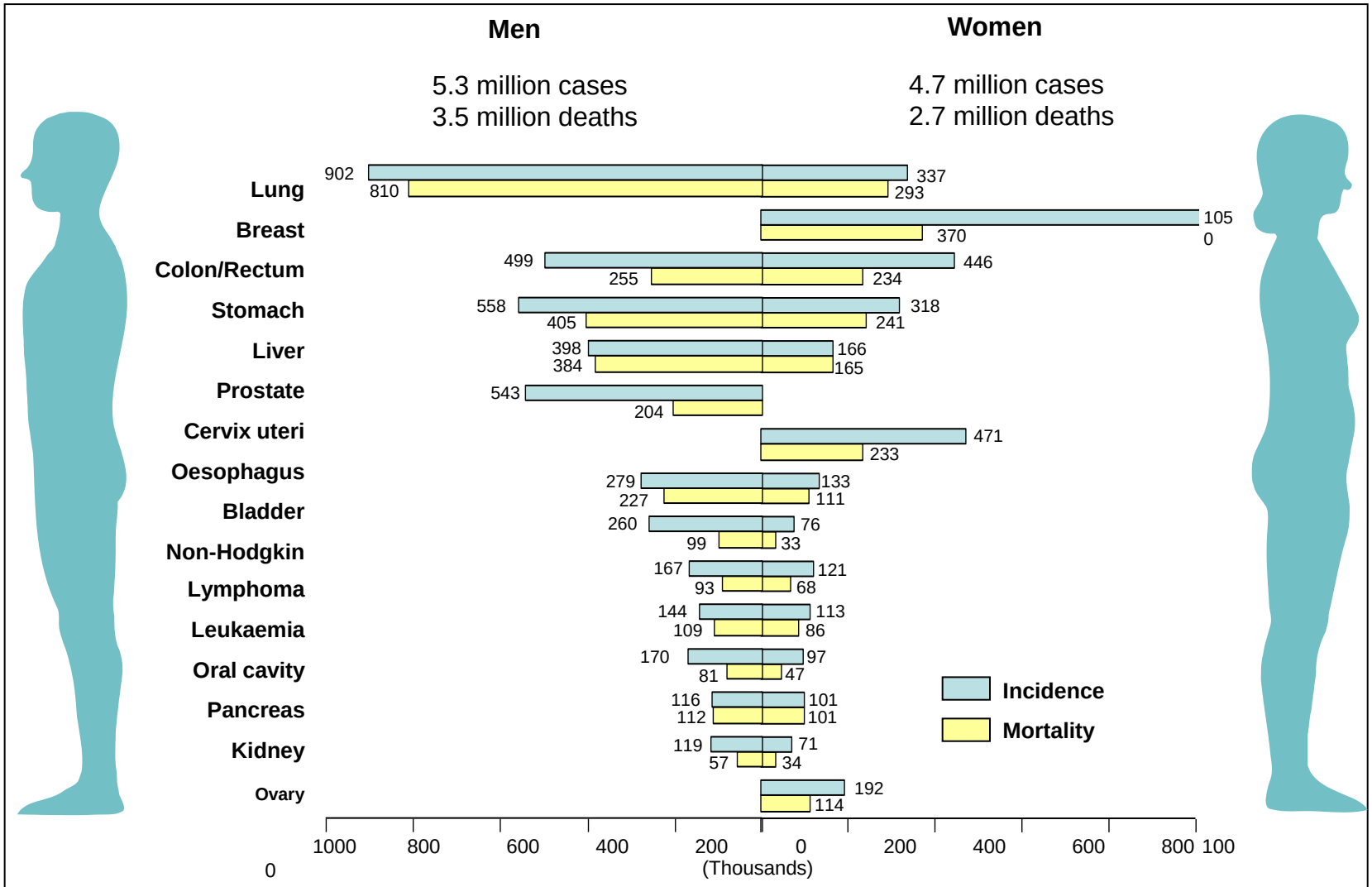
Cancer in General

- **There is no such thing as one “cancer”**
  - “Cancer” is an umbrella term for many, very different, diseases
  - On histological grounds, we distinguish > 400 different types of cancers
- **Cancer in the lay perception stands for:**
  - “Malignant neoplastic disorder” in scientific terms
  - Neoplasia = abnormal cell growth
- **Cancer is as ancient as mankind**
  - The world's oldest documented case of cancer hails from ancient Egypt, in 1500 BC
  - The details were recorded on a papyrus, documenting 8 cases of tumors occurring on the breast.

Cancer Statistics

- 10 million cases are detected each year
- 6.2 million people will die from cancer
- 20.4 million people living with cancer in the world today
- 1 in 3 people will be diagnosed with cancer in the UK and 1 in 4 will die from their disease

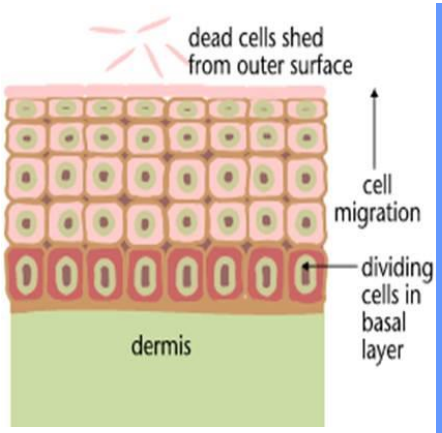
Cancer Statistics

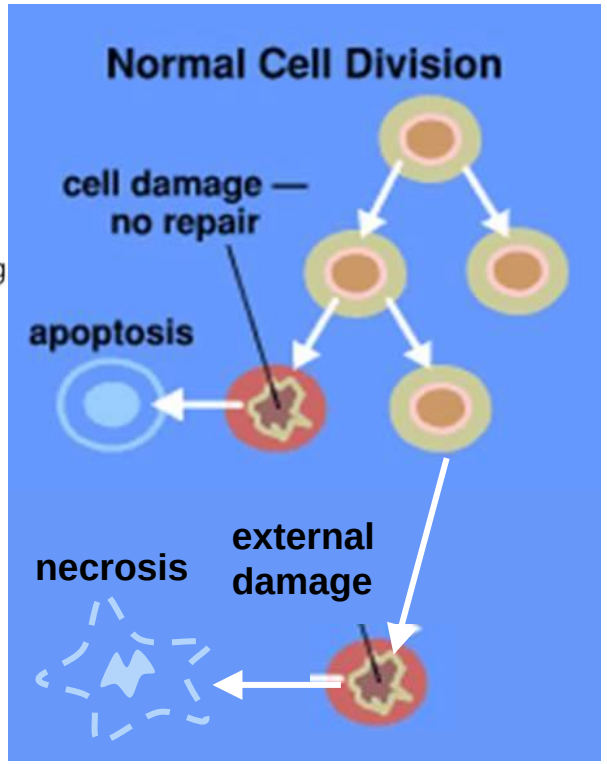


From: D.M. Parkin *The Lancet Oncology* 2: 533-543 (2001)

Cancer

- **The division of normal cells is precisely controlled.**
  - New cells are only formed for growth or to replace dead ones.
  - Cells that are old or not functioning properly normally self destruct (apoptosis) and are replaced by new cells.

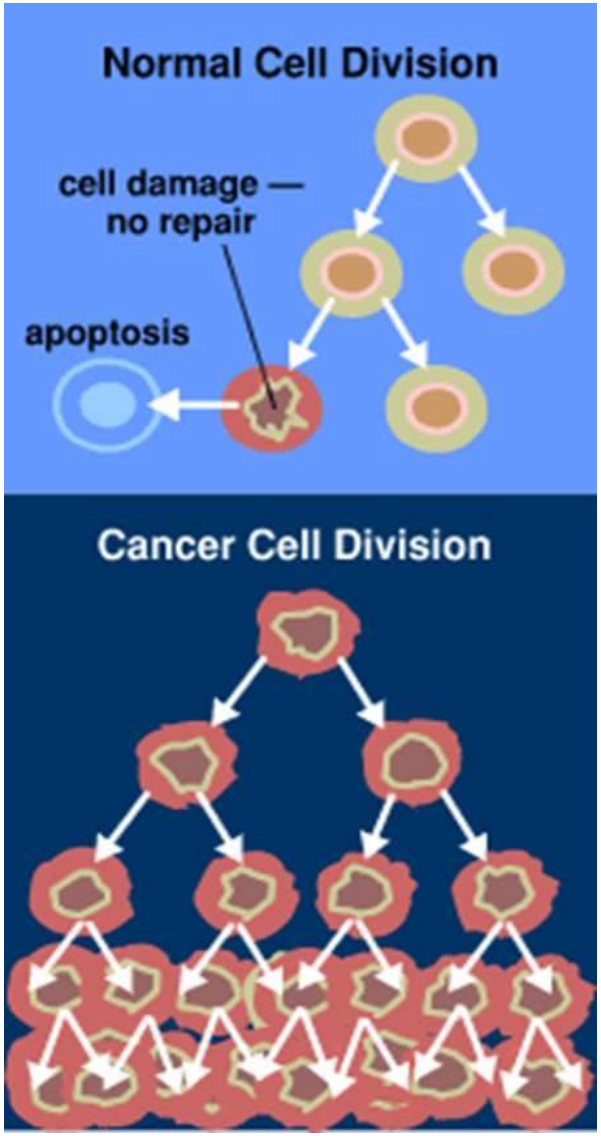




	Apoptosis	Necrosis
Natural	Yes. Naturally occurring cause of cellular death. Programmed cell death (PCD) in humans & multicellular organisms.	No. Caused by factors external to the cell or tissue, such as infection, toxins, or trauma
Effects	Beneficial	Detrimental
Result	Can prevent tumor formation (homeostatis between cell death rate and mitosis rate)	Necrosis results in inflammation, which could become chronic.

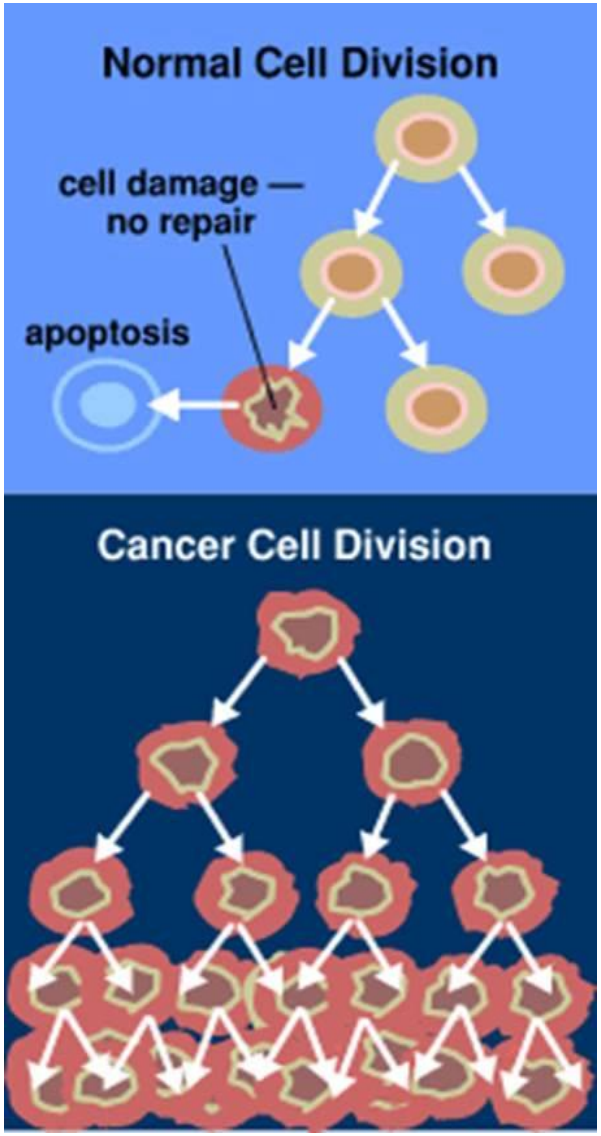
Cancer

- **Cancerous cells divide repeatedly out of control even though they are not needed**
  - They crowd out other normal cells and function abnormally
  - They can also destroy the correct functioning of major organs.
- **What is wrong with a cancer cell?**
  - Problems in the cell cycle
    - limitless replicative potential
  - Problems with normal cell death
    - evading normal apoptosis
  - Problems with “understanding” of signals from the outside:
    - insensitivity to anti-growth signals
    - self-sufficiency in growth signals
  - New “competences”:
    - neo-vascularisation
    - motility and invasive capacity
    - metastasis



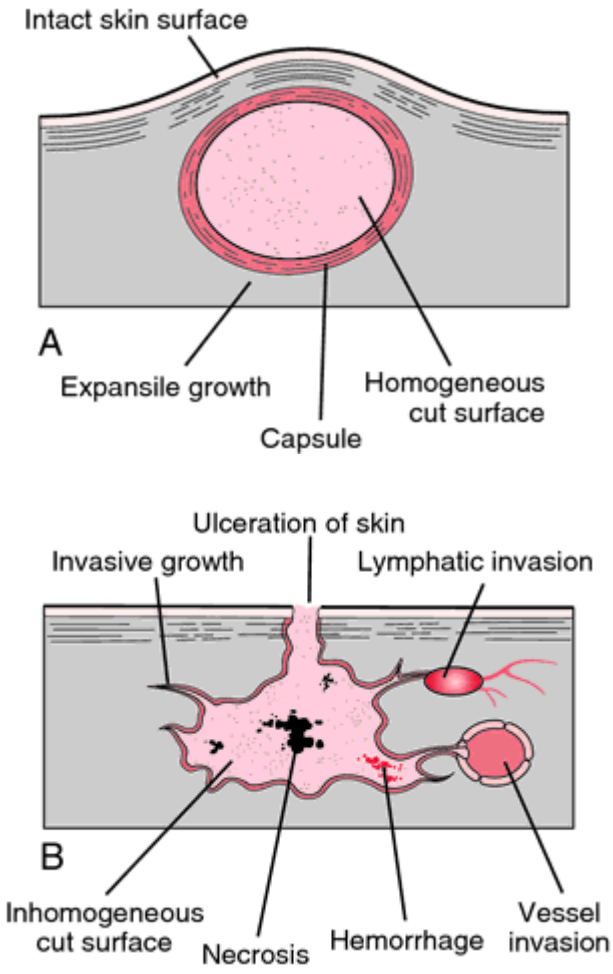
The Six Hallmarks of Cancer

- **Self-sufficiency in growth signals**
  - Constitutively activated growth factor signalling
- **Resistance to anti-growth signals**
  - Inactivated cell cycle checkpoint
- **Immortality (Evading apoptosis)**
  - Inactivated cell death pathway
  - Evading apoptosis
- **Resistance to cell death**
  - Activated anti- cell death signalling
  - Limitless reproductive potential
- **Sustained angiogenesis**
  - Activated VEGF signalling
- **Tissue invasion and metastases**
  - Loss of cell-to-cell interactions, etc.



Benign or malignant?

- **Benign tumors**
  - do not spread from their site of origin (capsule), but can crowd out (squash) surrounding cells eg brain tumor, warts.
- **Malignant tumors**
  - can spread from the original site and cause secondary tumors. This is called metastasis. They interfere with neighboring cells and can block blood vessels, the gut, glands, lungs etc.
- **Tumor Burden**
  - Both types of tumor can tire the body out as they both need a huge amount of nutrients to sustain the rapid growth and division of the cells.



What causes cancer?

- **Cancer arises from the mutation of a normal gene.**
  - Oncogenes are activated
    - Normal function: cell growth, gene transcription
  - Tumor suppressor genes are inactivated
    - Normal function: DNA repair, cell cycle control, cell death
  - It is thought that several mutations need to occur to give rise to cancer
- **A factor which brings about a mutation is called a mutagen.**
  - A mutagen is mutagenic.
  - Any agent that causes cancer is called a carcinogen and is described as carcinogenic.
- **So some mutagens are carcinogenic.**

What causes cancer?

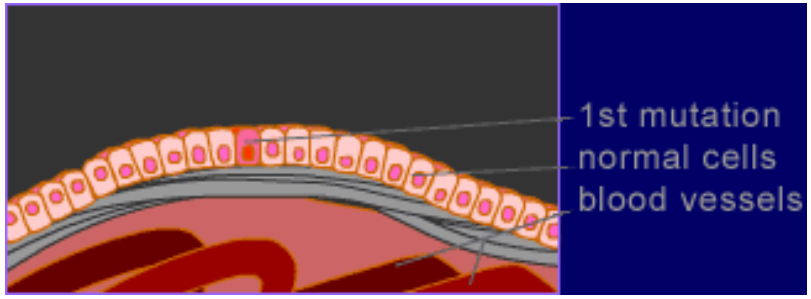
- **Tumor suppressor genes**
  - “Guardian(s) of the genome”
  - Often involved in maintaining genomic integrity (DNA repair, chromosome segregation)
  - Mutations in tumor suppressor genes lead to the “mutator phenotype”—mutation rates increase
  - Often the 1st mutation in a developing cancer
- **p53 - a classic tumor suppressor**
  - “The guardian of the genome”
  - Senses genomic damage
  - Halts the cell cycle and initiates DNA repair
  - If the DNA is irreparable, p53 will initiate the cell death process

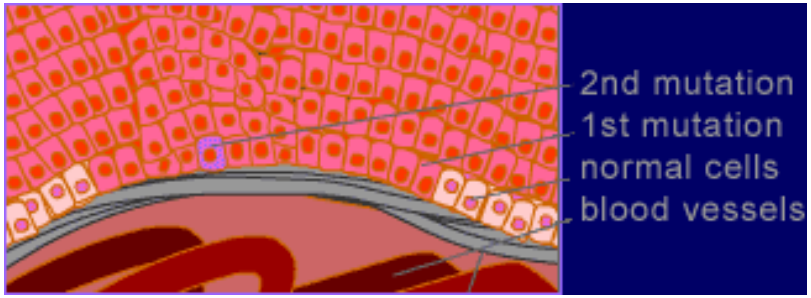
What causes cancer?

- **Oncogenes**
  - Mutated versions of proto-oncogenes
  - Proto-oncogenes are normal genes involved in cell growth and differentiation
  - Once mutated, they become oncogenes, which can cause cancer by helping the cells avoid cell death
- **HER2/neu—an oncogene**
  - A growth factor receptor
  - 25-30% of breast cancers over-express HER2/neu
  - Herceptin is used as a treatment
    - monoclonal antibody that interferes with the HER2/neu receptor

What causes cancer?

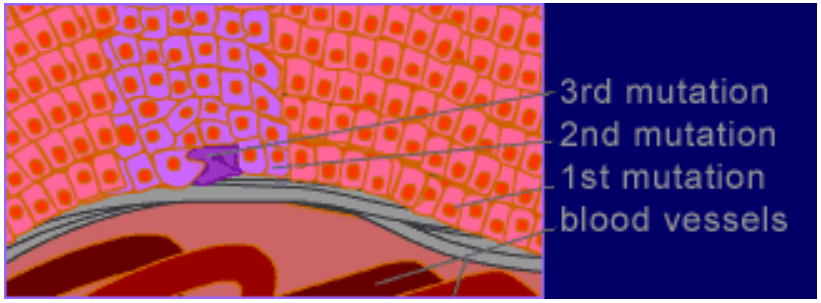
- **First Mutation**
  - A genetic mutation will cause a cell and its descendants to reproduce even though replacement cells are not needed.
  - The genetically altered cells have, over time, reproduced unchecked, crowding out the surrounding normal cells.
  - The growth may contain one million cells and be the size of a pinhead. At this point the cells continue to look the same as the surrounding healthy cells. (Hyperplasia)
- **Second Mutation**
  - After about a million divisions, there's a good chance that one of the new cells will have mutated further. This cell, now carrying two mutant genes, could have an altered appearance and be even more prone to reproduce unchecked.

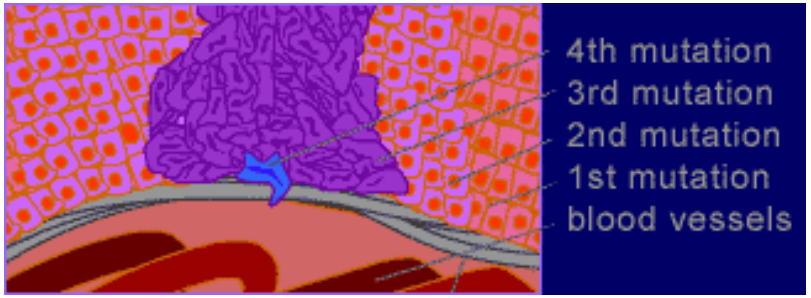




What causes cancer?

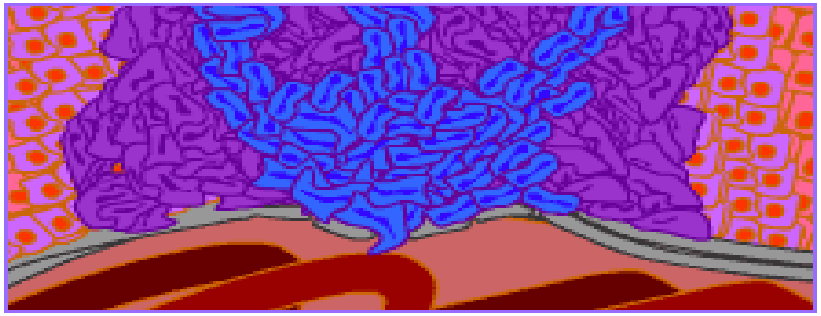
- **Third Mutation**
  - Over time and after many cell divisions, a third mutation may arise. If the mutation gives the cell some further advantage, that cell will grow more vigorously than its predecessors and thus speed up the growth of the tumour.
- **Fourth Mutation**
  - The new type of cells grow rapidly, allowing for more opportunities for mutations. The next mutation paves the way for the development of an even more aggressive cancer.
  - At this point the tumour is still contained.





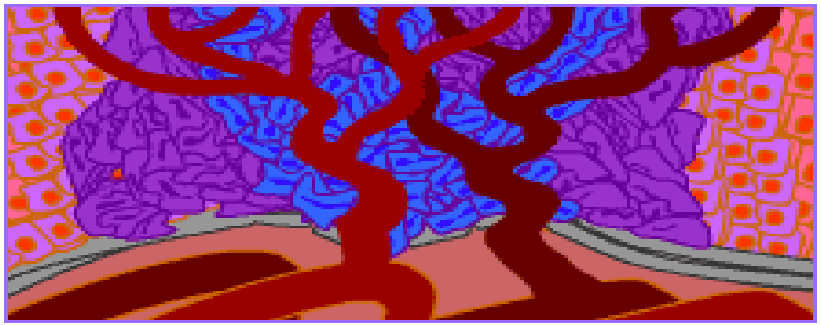
What causes cancer?

- **Breaking through the basement membrane**
  - The newer, wilder cells created by another mutation are able to push their way through the epithelial tissue's basement membrane
    - A meshwork of protein that normally creates a barrier.
  - The invasive cells in this tumour are no longer contained.
  - At this point the cancer is still too small to be detected.



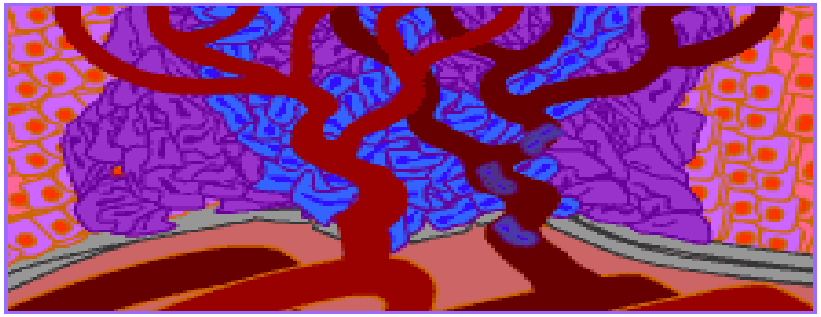
What causes cancer?

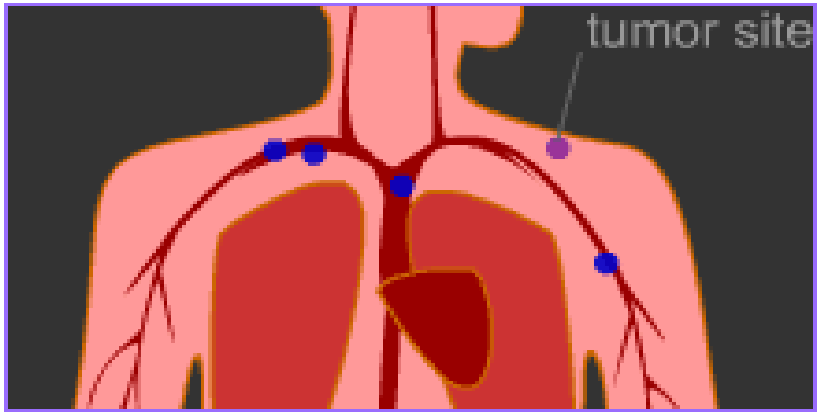
- **Angiogenesis**
  - Often during the development of earlier stages of the tumour, or perhaps by the time the tumour has broken through the basement membrane (as pictured above), angiogenesis takes place.
  - Angiogenesis is the recruitment of blood vessels from the network of neighbouring vessels.
  - Without blood and the nutrients it carries, a tumour would be unable to continue growing.
  - With the new blood supply, however, the growth of the tumour accelerates
  - It soon contains thousand million cells and, now the size of a small grape, is large enough to be detected as a lump



What causes cancer?

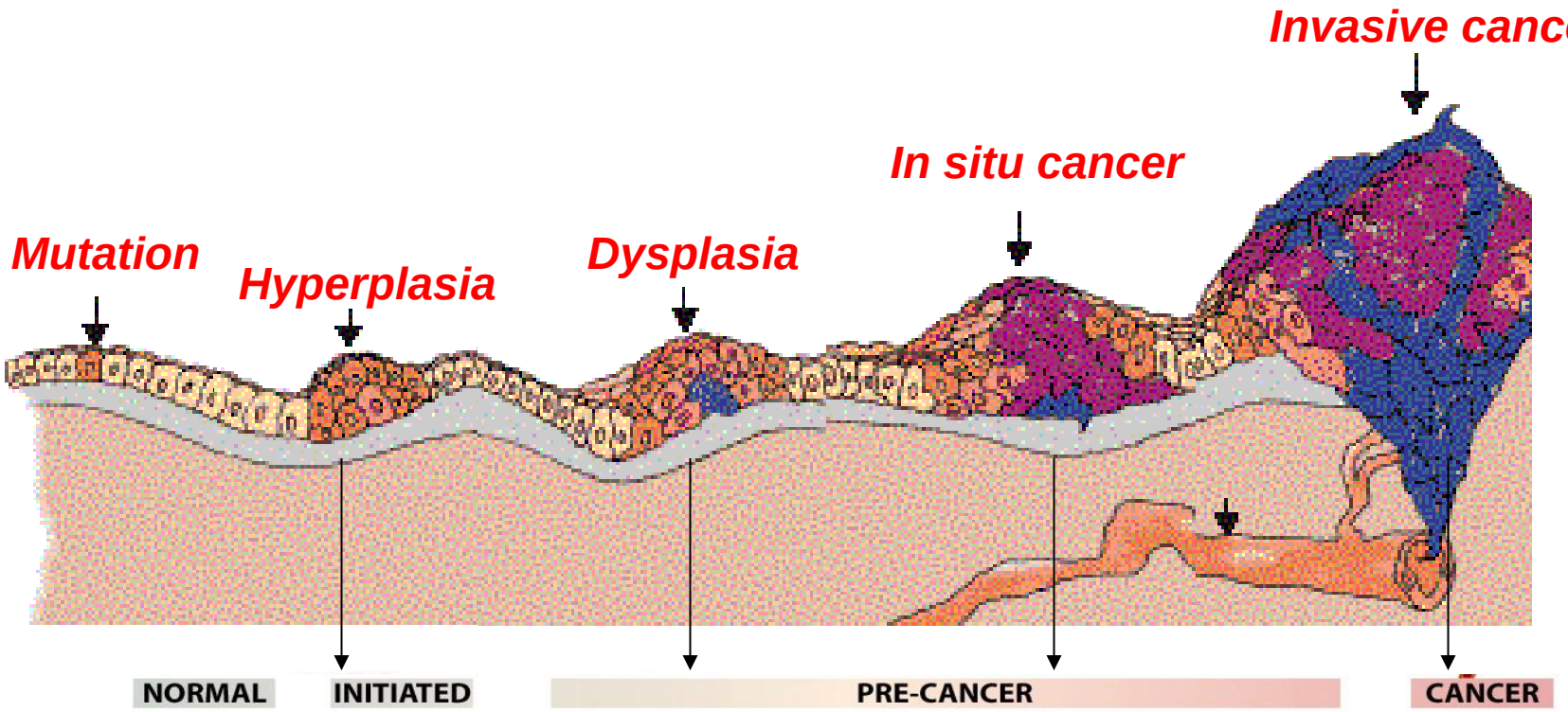
- **Metastasis**
  - What makes most tumors so lethal is their ability to metastasize
    - i.e. establish new tumor sites at other locations throughout the body → Secondary tumors
    - A tumor as small as a gram can send out a million tumor cells into blood vessels a day.
    - Most of these cells will die soon after entering the blood or lymph circulation.
  - To form a secondary tumor, a tumor cell must invade the tissue. It needs to
    - Detach from the original tumor site
    - Enter the newly formed circulation
    - Travel to other parts of the body
    - Leave the vessel system
    - Attach itself to a vessel's wall.
    - Work its way through the vessel
    - Enter the tissue.
  - Although perhaps less than one in 10,000 tumor cells will survive long enough to establish a new tumor site, a few survivors can escape and initiate new colonies of the cancer.





The first site of metastasis are usually the lymph nodes into which the primary site is draining into

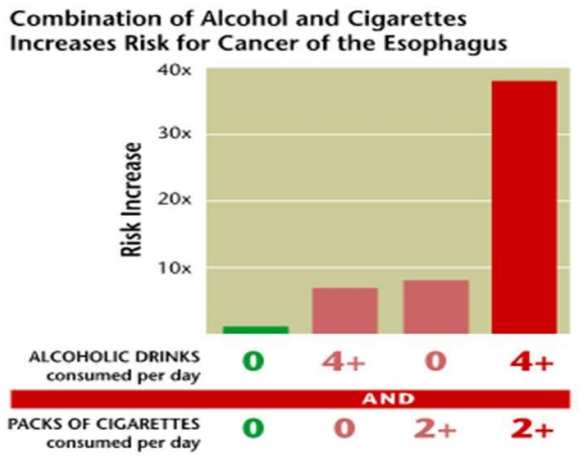
Cancerous growth



colon	5–20 years	adenoma	5–15 years			
head and neck	tobacco use 4–10 years	dysplastic oral leukoplakia	6–8 years			
cervix	CIN 1	9–13 years	CIN 3/CIS	10–20 years		
lung (smokers)	20–40 pack-years					
breast	atypical hyperplasia	DCIS	6–10 years			
prostate	20 years	PIN	≥10 years	latent cancer	3–15 years	

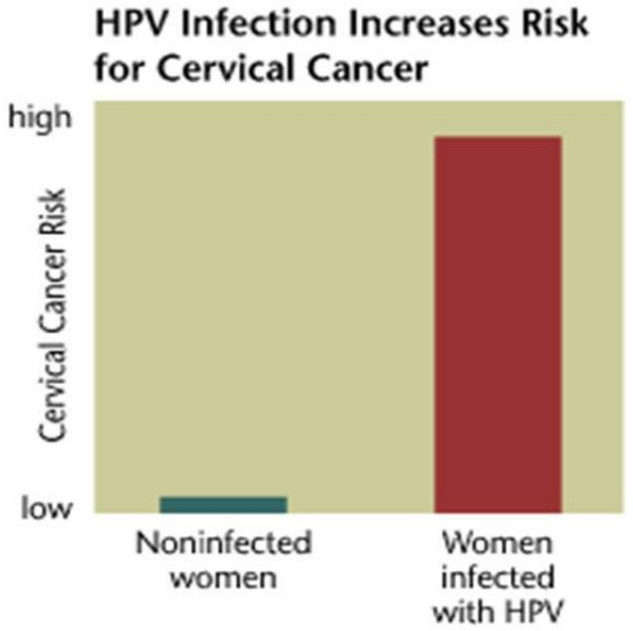
What causes carcinogenesis?

- **Ionising radiation**
  - X Rays, UV light
  - Single and double strand DNA breaks
- **Chemicals**
  - Alcohol
  - Asbestos
  - Wood dust
  - Rubber, plastics, dyes
  - Tar / bitumen
  - Aflatoxin
  - Alkylating agents
  - Industrial polution
  - Tobacco
    - Single biggest cause of cancer
    - 25-40% smokers die in middle age
    - 9 in 10 lung cancers
    - Know to cause cancer in 1950



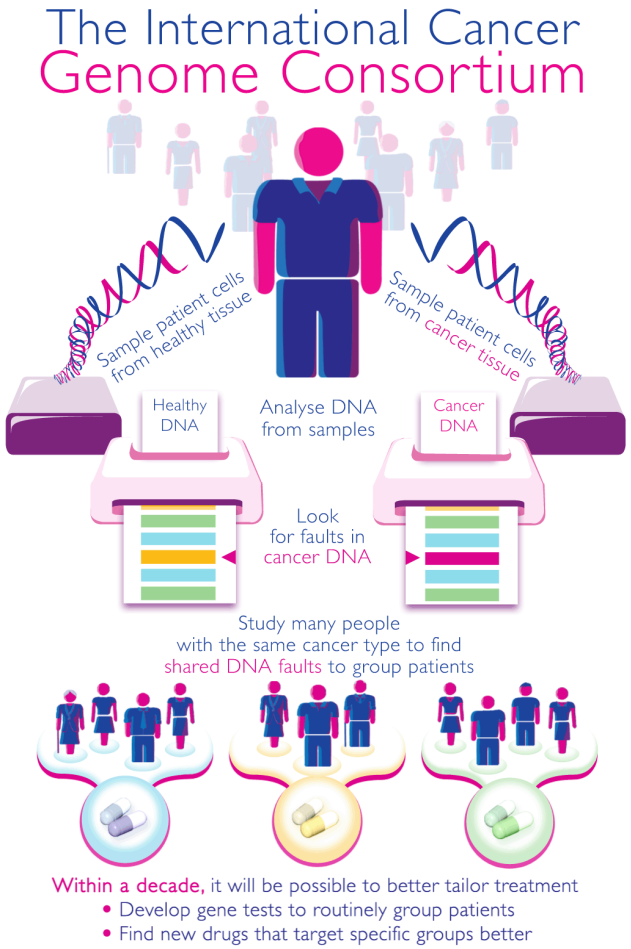
What causes carcinogenesis?

- **Immunity and Virus infection**
  - HIV / AIDS
  - Immunosuppression
  - Hepatitis B
  - Human T-cell Leukaemia virus
  - Epstein Barr Virus
  - Human Papilloma Virus (HPV)
  - Etc
  - Estimated Burden of Cancer from Infection Worldwide in 2000:
    - 1,801,000 cases (17.9 %)



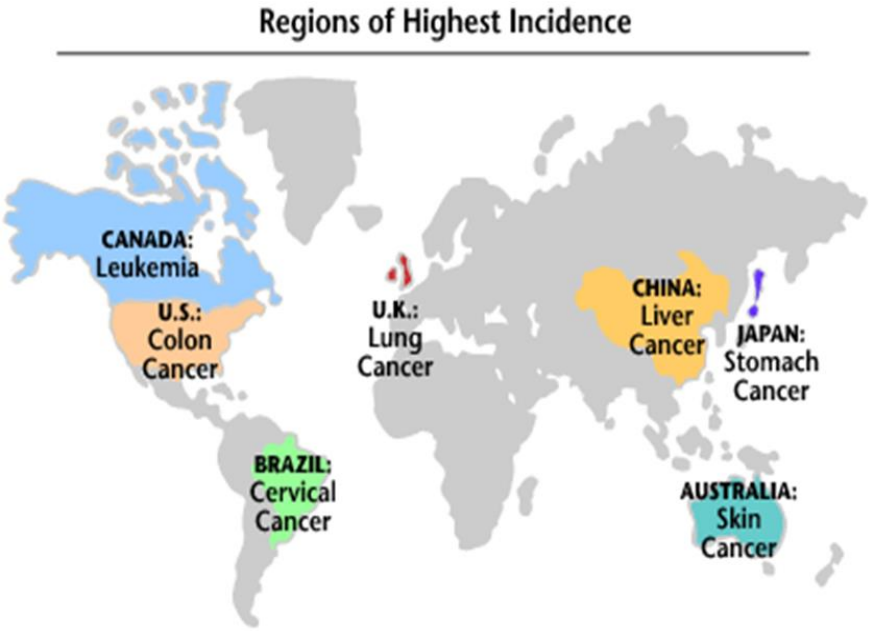
What causes carcinogenesis?

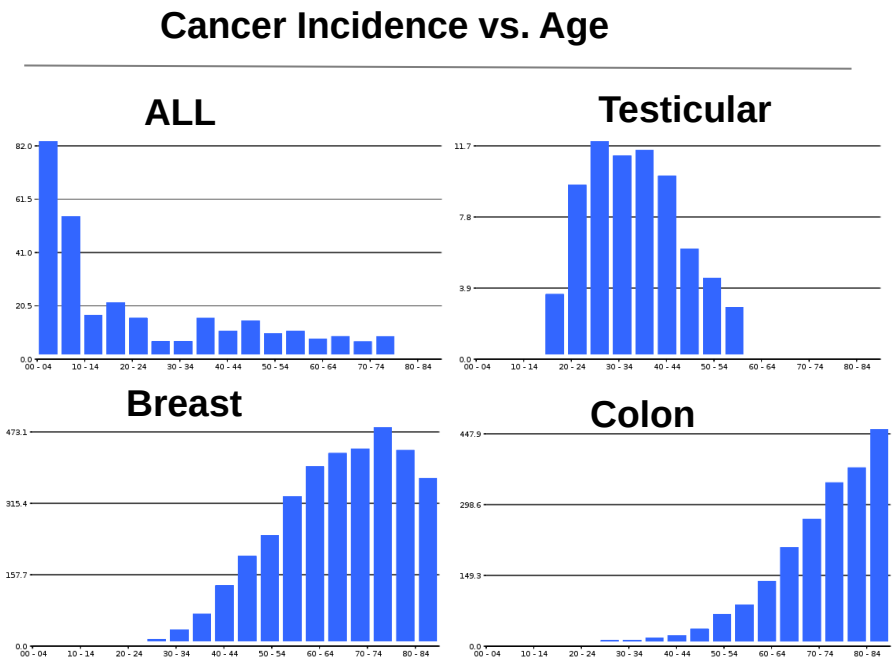
- **Hereditary predisposition**
  - Some families are more susceptible to getting certain cancers.
  - Remember you can't inherit cancer its just that you maybe more susceptible to getting it.
  - 5-10% of Cancers
  - Genes isolated for several classic familial cancer syndromes:
    - RB1 (retinoblastoma)
    - APC (familial polyposis)
    - Human Non Polyposis Colon Cancer (HNPCC)
    - BRCA 1&2 (breast cancer)
    - p53 (many cancers)

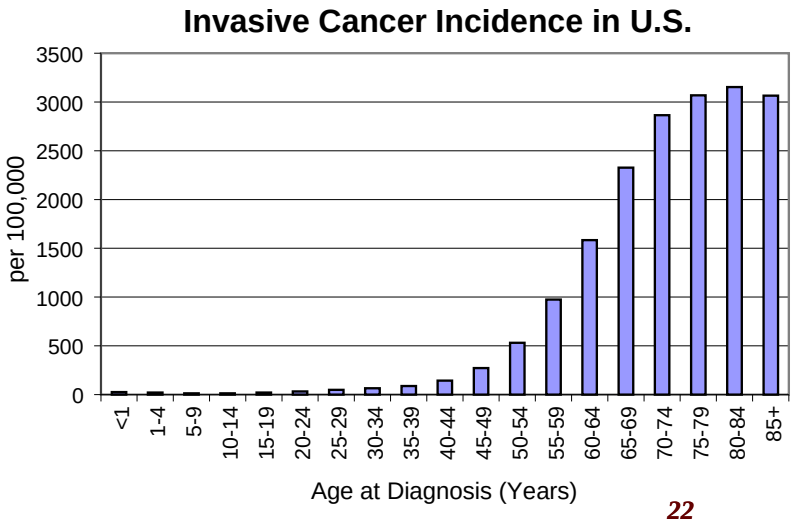


What causes carcinogenesis?

- **Lifestyle:**
  - Age
  - Occupation
  - Location
  - Ethnicity







What causes carcinogenesis?

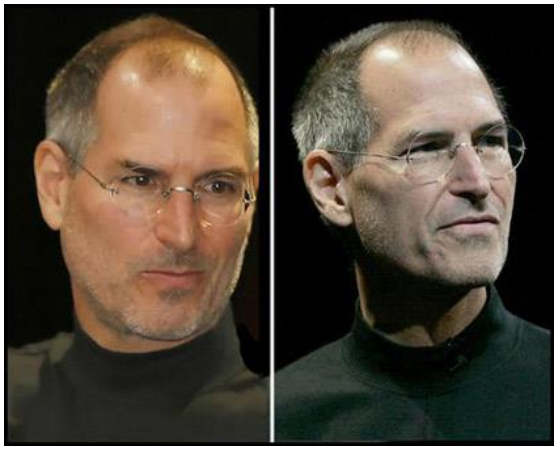
- **Lifestyle:**
  - Highly caloric diet, rich in fat, refined carbohydrates and animal protein
  - Low physical activity
  - Consequences:
    - Cancer
    - Diabetes
    - Cardiovascular disease
    - Hypertension

Diagnosis and Staging

Symptoms
- Weight loss
- Rectal bleeding
- Persistent cough
- Pain

Screening
- Pap smear
- Mammogram
- Endoscopy
- Occult blood

Incidental
- Radiology
- > ~1 gm (10^9 cells)



Biopsy

Histopathology

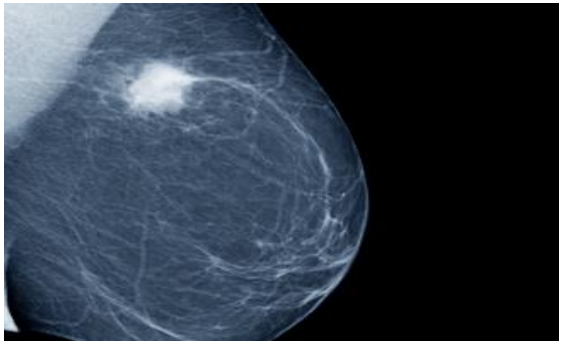
Staging

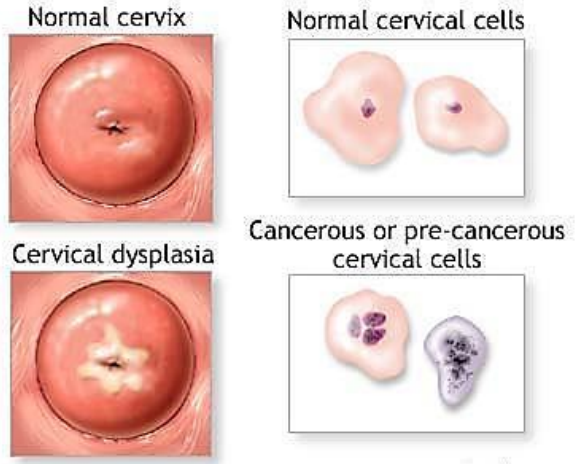
Autopsy

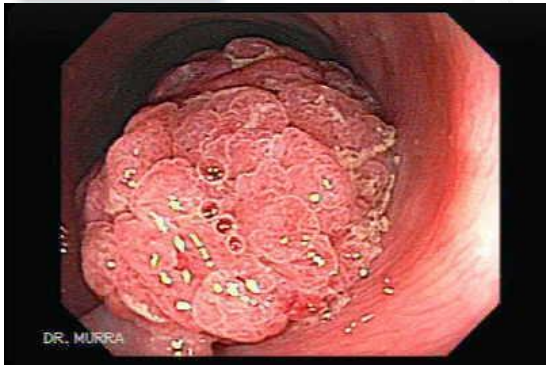
Diagnosis and Staging

Screening

- **Unfortunately, most cancers become symptomatic when it is too late!**
- **Screening**
  - The use of simple tests across a healthy population in order to identify individuals who have disease, but do not yet have symptoms.
- **Not all screening test are cost-effective (or effective)**
- **Based on the existing evidence, mass population screening can be advocated only for**
  - Breast cancer
    - Mammography (x-ray)
  - Cervical cancer
    - Cytology (Papanicolaou Smear)
  - Colon Cancer (?)
    - Endoscopy every 1, 5, or 10 years
  - Prostate cancer (???)
    - Digital exam and blood test (prostate specific antigen – PSA)
- **More methods are currently being developed**







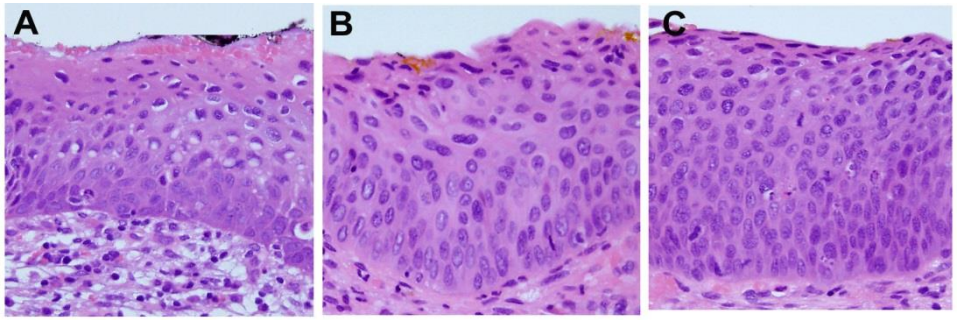
Diagnosis and Staging

Diagnosis

- **Clinical History**
- **Diagnostic procedures**
  - Imaging (X-Ray, CT, MRI, US, Endoscopy)
  - Blood tests
  - Biopsy (guided biopsy) →Histopathology
- **Pathological staging**
  - **G** (1-4): the grade of the cancer cells
  - "low grade" if they appear similar to normal cells
  - "high grade" if they appear poorly differentiated

CT Guided Biopsy

Cervical Intraepithelial Neoplasia



Diagnosis and Staging

TNM Staging

- **T (0,1-4): size or direct extent of the primary tumor**
- **N (0-3): degree of spread to regional lymph nodes**
  - N0: tumor cells absent from regional lymph nodes
  - N1: tumor cells spread to closest or small number of regional lymph nodes
  - N2: tumor cells spread to an extent between N1 and N3.
  - N3: tumor cells spread to most distant or numerous regional lymph nodes
- **M (0/1): presence of metastasis**
  - M0: no distant metastasis
  - M1: metastasis to distant organs (beyond regional lymph nodes)

Diagnosis and Staging

- **Staging is very important**
  - Determines prognosis
  - Determines treatment

Figure 1.1: Relative five-year survival estimates based on survival probabilities observed during 2000-2001, by sex and site, England and Wales

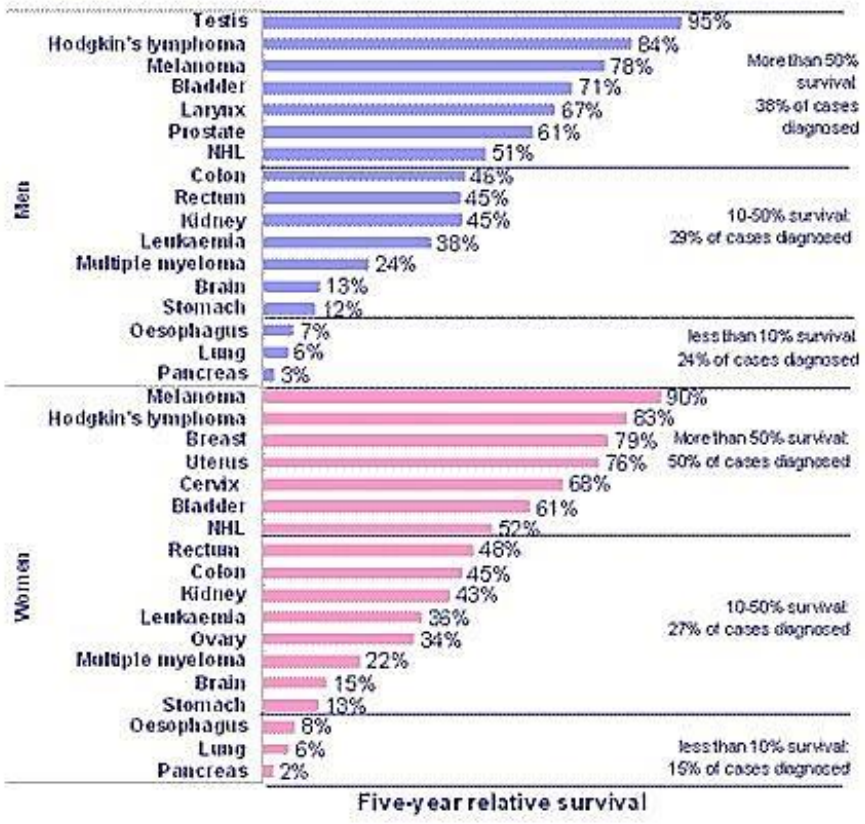
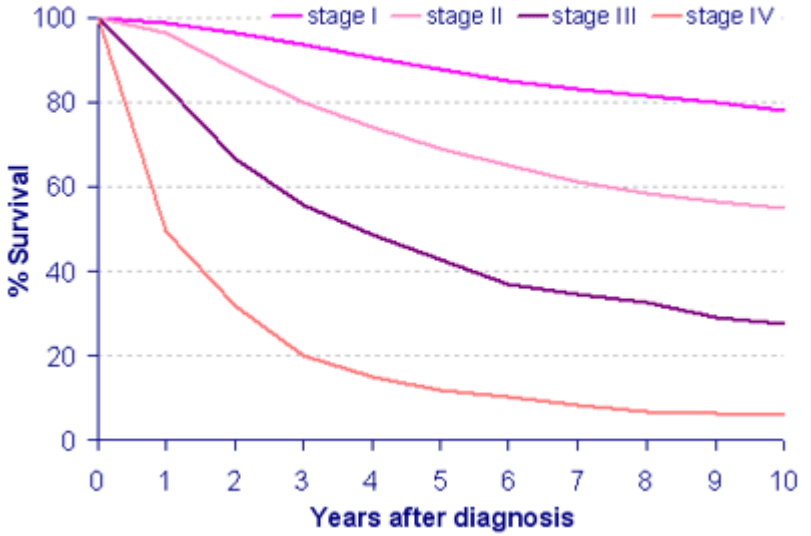


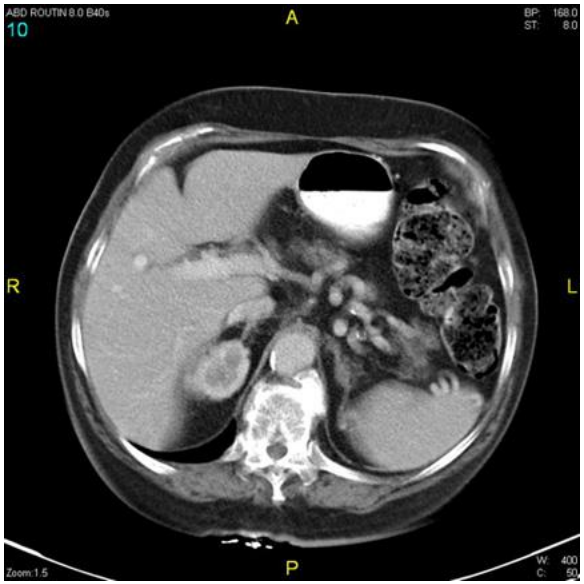
Figure 3.3: 0-10 year relative survival for cases of breast cancer by stage diagnosed in the West Midlands 1985-1989 followed up to the end of 1999, as at January 2002

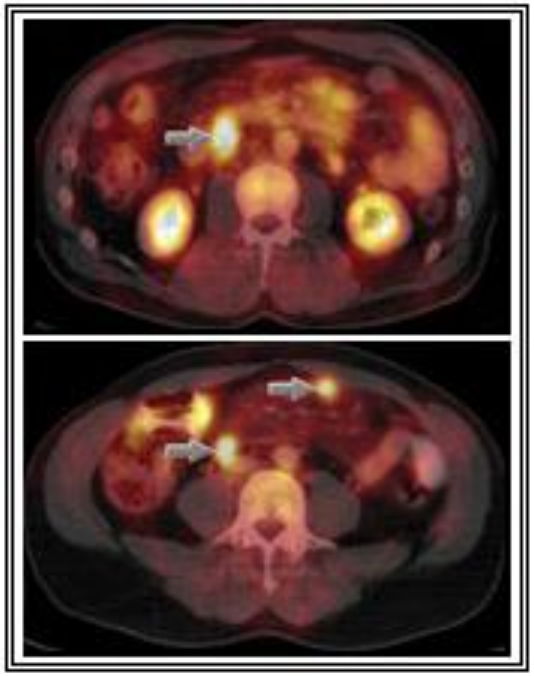


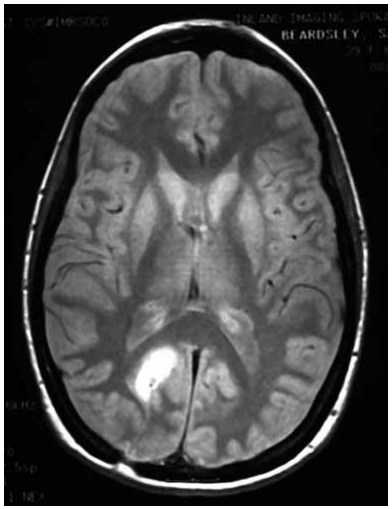
Imaging for Diagnosis and Staging

- **CT scan**
- **PET/CT**
- **SPECT/CT**
- **MRI**

- **Determine**
  - Staging
  - Response

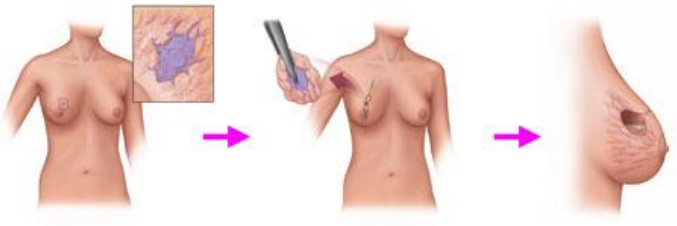




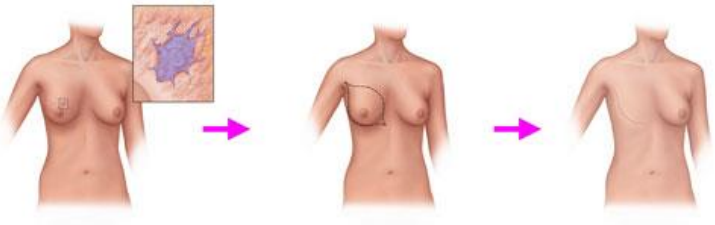


What can cancer therapies target?

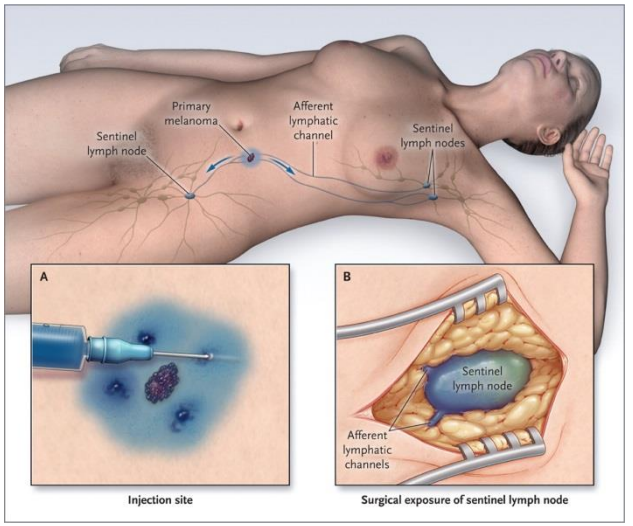
- **Surgery**
  - Remove as much tumor as possible
    - Curative or Palliative
  - Very important to
    - Get clean tumor margins
    - Examine and remove lymph nodes
  - Many times followed by other therapies to reduce the risk of metastasis



Lumpectomy: surgical removal of the cancerous lump



Mastectomy: surgical removal of the entire breast



What can cancer therapies target?

- **Classic cancer therapies kill rapidly dividing cells**
  - Target the DNA
    - Ionizing radiation
    - Chemotherapy
- **Radiation**
  - External beam radiation (Gamma photons, Neutron beams)
  - Radioimmunoconjugates (Antibody targeted radiation)
  - Free isotopes (^{131}I, Gallium)
- **Chemotherapy**
  - Various agents
  - Often used in combinations
    - Minimize resistance
    - Reduces toxicity
  - Can be curative in specific cases
    - AML, ALL, HD, NHL, Testicular cancer
- **Many and severe side effects**
  - Hair loss
  - Weakened immune system
  - Problems with the gastointestinal tract

What can cancer therapies target?

- **Modern, targeted therapies attack specific proteins that are abnormally expressed in a tumor**
  - May block over-expressed growth factor receptors → Herceptin
  - Generally, there are few side effects since these therapies are specifically targeted to cancer cells
  - Antibodies
    - Target specific antigen
    - Specificity is relative
  - Small molecules
    - Target oncogene product
    - Inhibit signaling at key steps
    - Safer than chemotherapy
    - Specific side effects
    - Specificity is often relative

- **A person's immune system will not target tumor cells because they appear to be "self"**
  - Some new therapies focus on activating one's immune system against a cancer

What can cancer therapies target?

- **Adjunctive**
  - Tumor cells do not live in isolation
- **Hormonal therapy**
  - medicines treat hormone-receptor-positive cancers
    - lowering the amount of the hormone in the body
    - blocking the action of the hormone on cancer cells
  - Hormonal therapy medicines are NOT effective against hormone-receptor- negative cancers
- **Stroma**
  - Adhesion resistance
- **Blood vessels**
  - Angiogenesis inhibitors
    - Antibodies (Avastin)
    - Small molecules (Thalidomide, other IMiDs)
    - Too much anti-agiogenesis can prevent drugs from reaching the tumor
- **Immune system**
  - Vaccines
  - E.g. vaccine against HPV prevents most cervical cancers

10 Rules to Avoid Cancer

1. Don’t smoke
2. Don’t smoke.
3. Don’t smoke.
4. Avoid exposure to other known carcinogens, including aflatoxin, asbestos and UV light.
5. Enjoy a healthy diet, moderate in calories, salt and fat, and low in alcohol.
6. Eat fresh fruit and vegetables several times a day.
7. Be physically active and avoid obesity.
8. Have vaccination against, or early detection/treatment of, cancer causing chronic infections.
9. Have the right genes.
10. Have good luck !