The Basic Science of Oncology
A Clinician's Perspective

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Oncology 520

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Clinical Vignette #1

- Mr. Jones has gone to see his doctor because he has a cough.

Overview

- Cancer: How big is the problem
- How can we intervene?
- How is Diagnosis established?
- Cancer terminology
- What treatments are available and what can they offer?
- Conclusions

Cancer

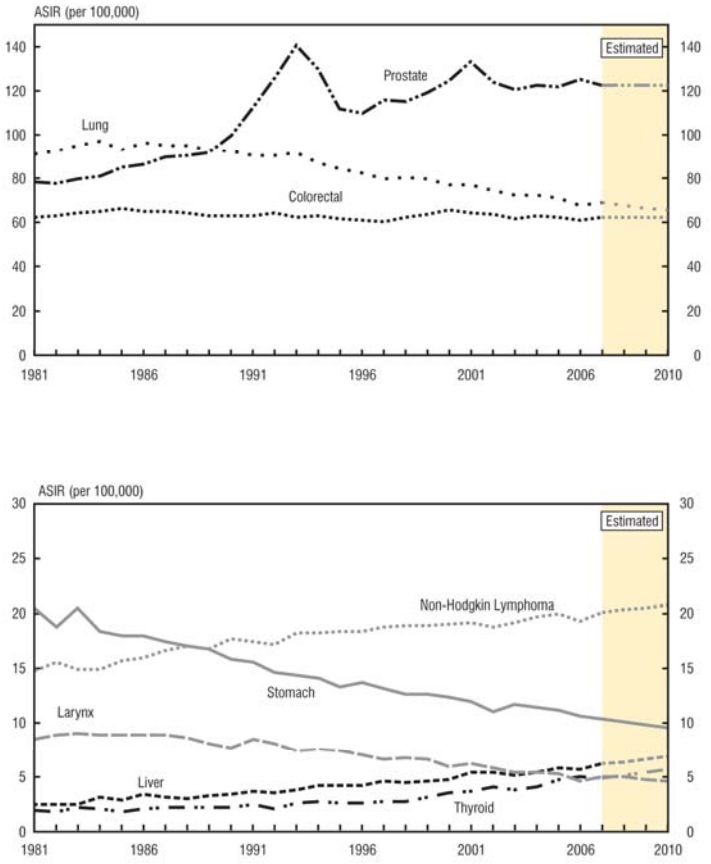
- What is cancer?
  - Neoplasia: new growth
  - Neoplasm: the actual lump of new tissue
  - Tumour: swelling

  - An actual definition of cancer is surprisingly hard to come up with
    - “a neoplasm of abnormal tissue, the growth of which exceeds and is uncoordinated with normal tissue and persists once the stimulus for its growth is removed

Incidence- Males

Figure 4.6

Age-Standardized Incidence Rates (ASIR) for Selected* Cancers, Males, Canada, 1981–2010



* Five most frequent cancers (both sexes combined) and cancers with a statistically significant change in incidence rate of at least 2% per year (see Table 4.5).

Note: Rates are age-standardized to the 1991 Canadian population. See Table 4.1 for data points. Actual data for incidence were available to 2006. The range of scales differs widely between the figures.

Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada

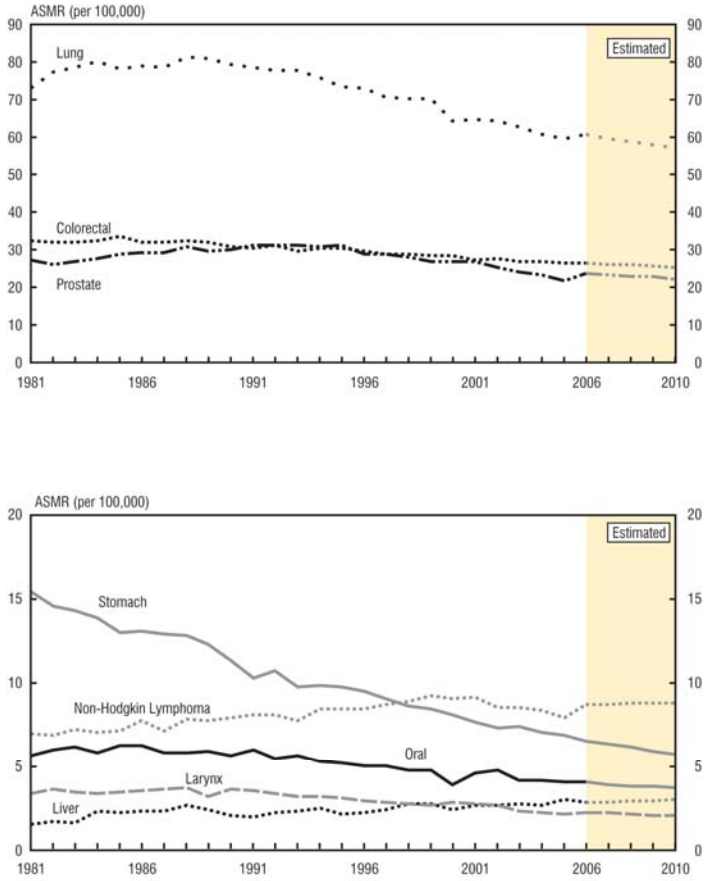
Data source: Canadian Cancer Registry database at Statistics Canada

Canadian Cancer Statistics 2010

Mortality- Males

Figure 4.7

Age-Standardized Mortality Rates (ASMR) for Selected* Cancers, Males, Canada, 1981–2010



* Five most frequent cancers (both sexes combined) and cancers with a statistically significant change in mortality rate of at least 2% per year (see Table 4.5).

Note: Rates are age-standardized to the 1991 Canadian population. See Table 4.2 for data points. Actual data for mortality were available to 2005. The range of scales differs widely between the figures.

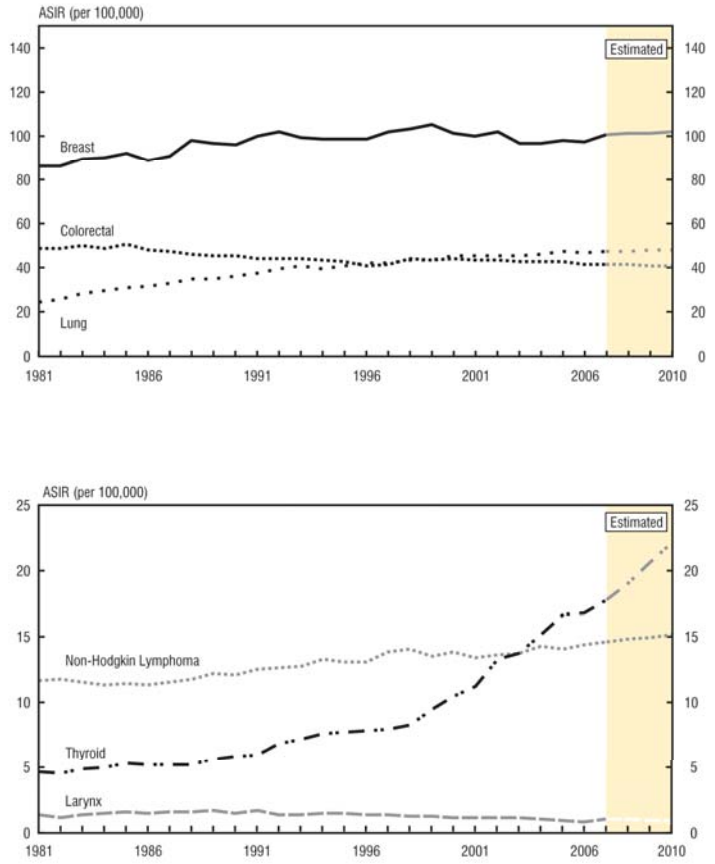
Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada

Data source: Canadian Vital Statistics Death database at Statistics Canada

Incidence- Females

Figure 4.8

Age-Standardized Incidence Rates (ASIR) for Selected* Cancers, Females, Canada, 1981–2010



* Five most frequent cancers (both sexes combined) and cancers with a statistically significant change in incidence rate of at least 2% per year (see Table 4.5).

Note: Rates are age-standardized to the 1991 Canadian population. See Table 4.3 for data points. Actual data for incidence were available to 2006. The range of scales differs widely between the figures.

Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada

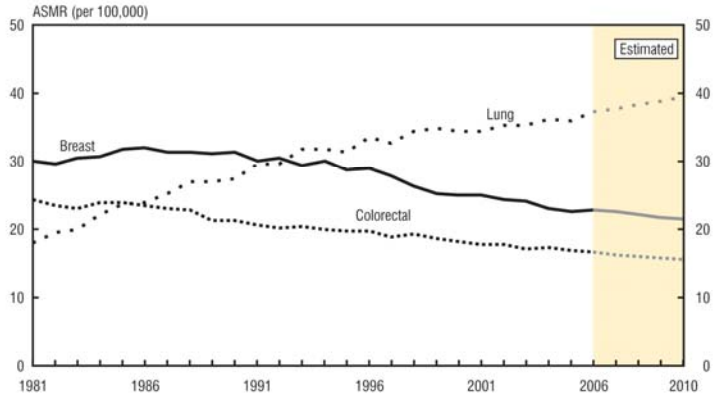
Data source: Canadian Cancer Registry database at Statistics Canada

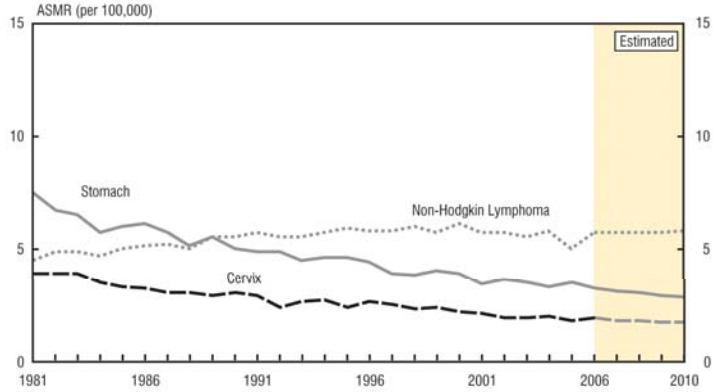
Canadian Cancer Statistics 2010

Mortality-Females

Figure 4.9

Age-Standardized Mortality Rates (ASMR) for Selected* Cancers, Females, Canada, 1981–2010





* Five most frequent cancers (both sexes combined) and cancers with a statistically significant change in mortality rate of at least 2% per year (see Table 4.5).

Note: Rates are age-standardized to the 1991 Canadian population. See Table 4.4 for data points. Actual data for mortality were available to 2005. The range of scales differs widely between the figures.

Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada

Data source: Canadian Vital Statistics Death database at Statistics Canada

Clinical Vignette #2

- Mr. Jones returns to the clinic to find out about the results of his CXR

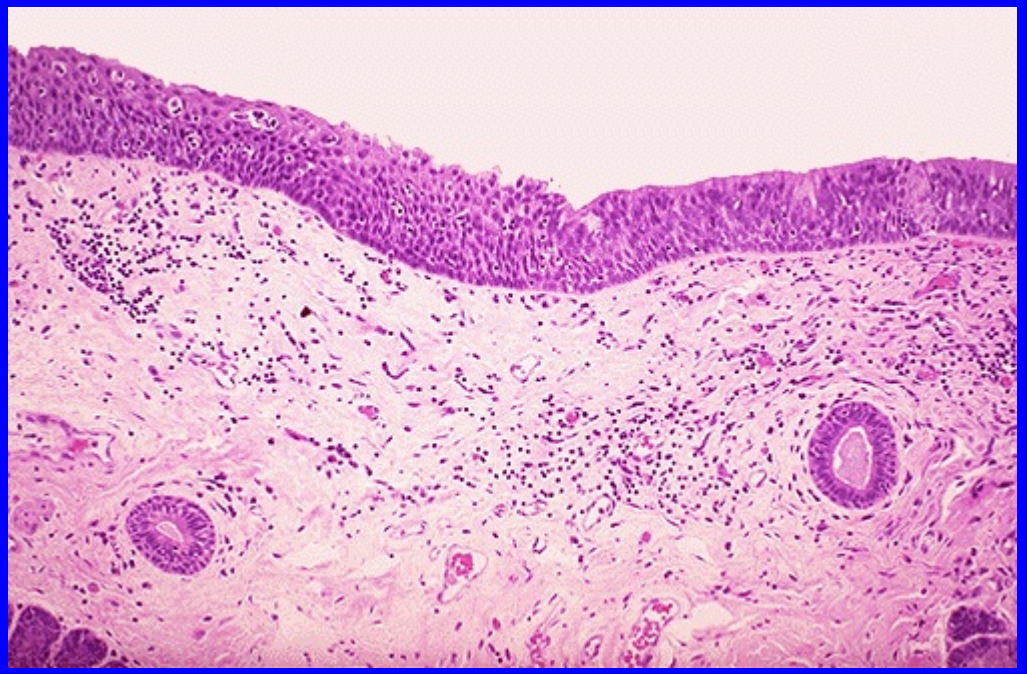
Areas for intervention

- Diagnosis
  - Earlier diagnosis should theoretically save lives
    - Mammogram, Pap smear, ?PSA for prostate
- Treatment
  - Better treatment modalities
    - RT, chemo, small molecules, monoclonal antibodies
- Prevention
  - Quit smoking, sunscreens

Premalignant Lesions

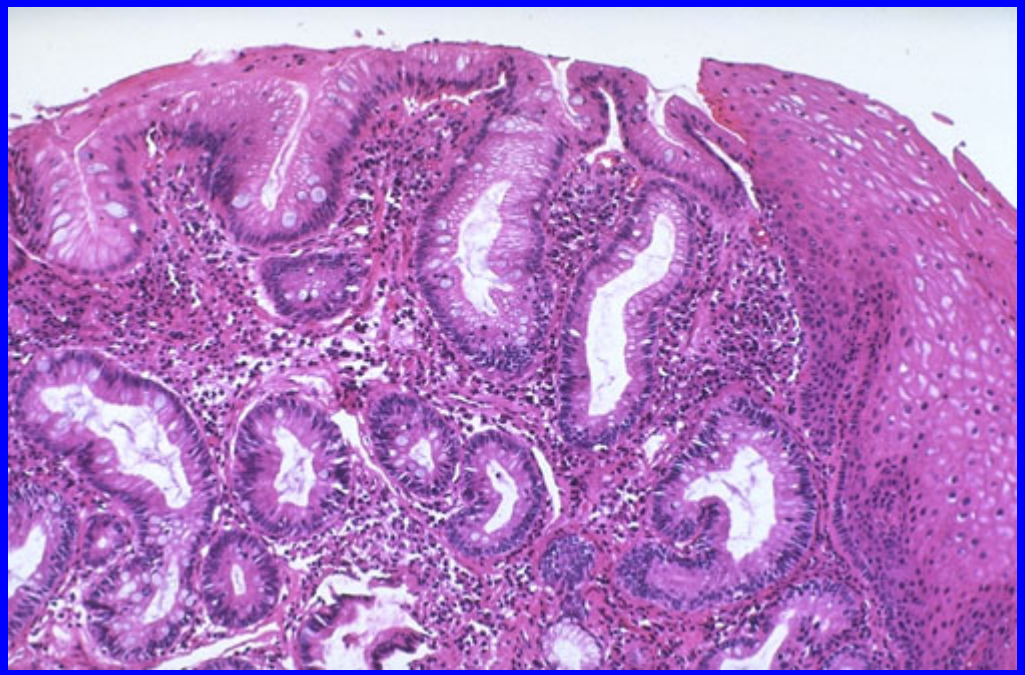
- Premalignant conditions also exist
  - Metaplasia: replacement of one normal epithelium with another, but in an unusual location
    - Reversible
  - Dysplasia: disordered growth and differentiation of an epithelium
    - reversible

Metaplasia



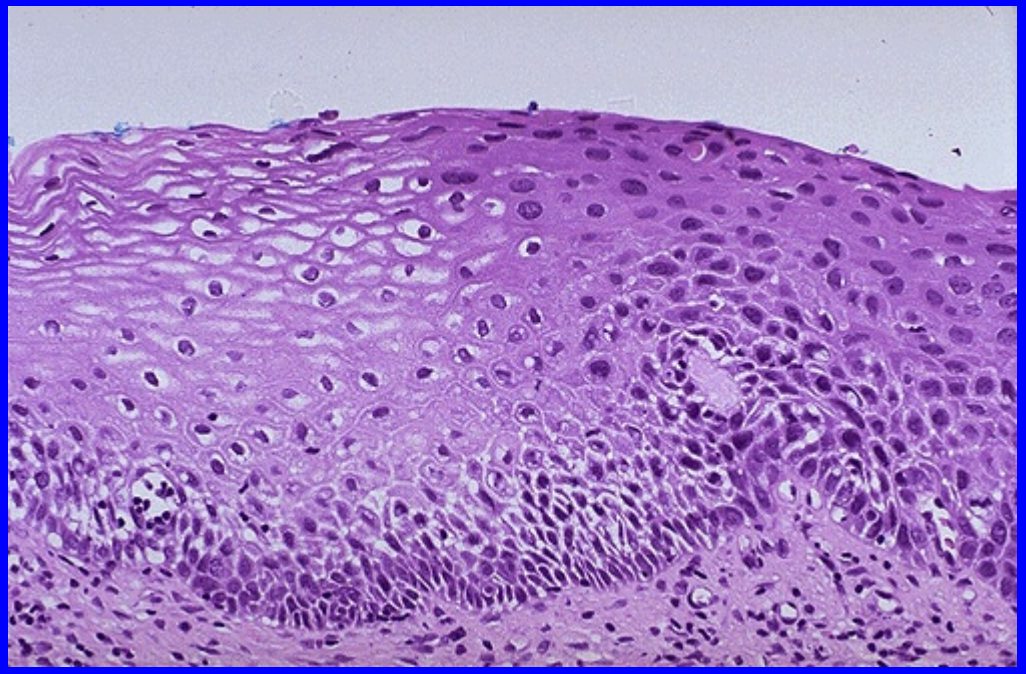
The first step toward neoplasia is cellular transformation. Here, there is metaplasia of normal respiratory laryngeal epithelium on the right to squamous epithelium on the left in response to chronic irritation of smoking.

Metaplasia



This biopsy of the lower esophagus in a patient with chronic gastroesophageal reflux disease shows columnar metaplasia (Barrett's esophagus), and the goblet cells are typical of an intestinal type of epithelium. Squamous epithelium typical of the normal esophagus appears at the right.

Dysplasia



At high magnification, the normal cervical squamous epithelium at the left merges into the dysplastic squamous epithelium at the right in which the cells are more disorderly.

Cancer Development

- From the first oncogenic insult to obvious cancer development can take years
- If inciting cause removed, reversal of the process may occur if early enough (during dysplastic phase)
  - E.g. quit smoking
- All of this occurs at a microscopic level
  - How do we know?
  - How can we detect it?

Detecting Cancer

- Clinicians have several ways they can detect cancer
  - Physical examination
    - Breast lump
  - Radiology testing
    - CXR shows a lung mass
  - Laboratory and special tests
    - Pap smears, bloodwork

Detecting Cancer

- Ability to detect cancer is dependent on having a large enough mass to find
  - 0.5 -1 cm mass approx. at lower limits of detection by radiology
  - 1 gram of tissue
  - This represents 10^9 cells
  - Physical examination even less sensitive
  - Lethal tumour burden is about 10^{12} cells

Cancer Detection

- Consider the growth kinetics
  - Original transformed cell: 10 microns
  - 30 doublings to get to 10^9 cells
  - 10 more doublings to get to 10^{12} cells

- For most solid tumours, the vast majority of the life cycle of the tumour is completed by the time it's detected
- If we wait for people to have symptoms, many will be too advanced to be cured

Screening

- Screening means testing asymptomatic people for an illness to see if they have it
- Cancer screening done for several illnesses
  - Cervix, breast, prostate, colon
- Most cancers have no viable screening options
  - Lung cancer

Screening
Why doesn't it always work?

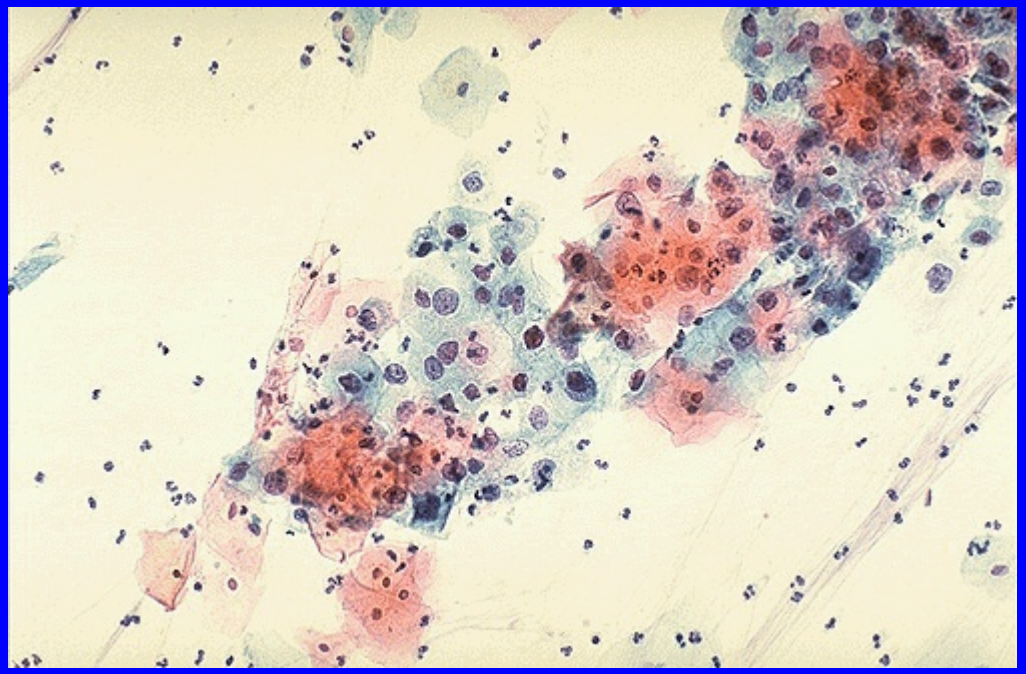
- Lead time bias
  - tests let you know you have a cancer but you can't do anything to change the natural outcome
    - The test lets you know sooner you have cancer but you can't do anything about it

- Length time bias
  - Tests tend to discover slow growing cancers that will never be a threat to the patient's life
    - If all you can detect are slow growing cancers, what's the point?

Screening

- What are some characteristics of a good screening test?
  - Important disease
  - Relatively non-invasive testing method
  - Good specificity and sensitivity
  - Treatment can be offered at an earlier stage that would affect the ultimate outcome

Pap Smear screening



Some epithelia are accessible enough, such as the cervix, that cancer screening can be done by sampling some of the cells and sending them to the laboratory. Here is a cervical Pap smear in which dysplastic cells are present that have much larger and darker nuclei than the normal squamous cells with small nuclei and large amounts of cytoplasm.

Diagnosis

- Since most tumours can’t be detected through screening, often they are only found after patients have symptoms
- Patients may undergo biopsy prior to surgery
- Surgical excision is usually required
- Pathologist then examines the specimen to determine malignancy or not

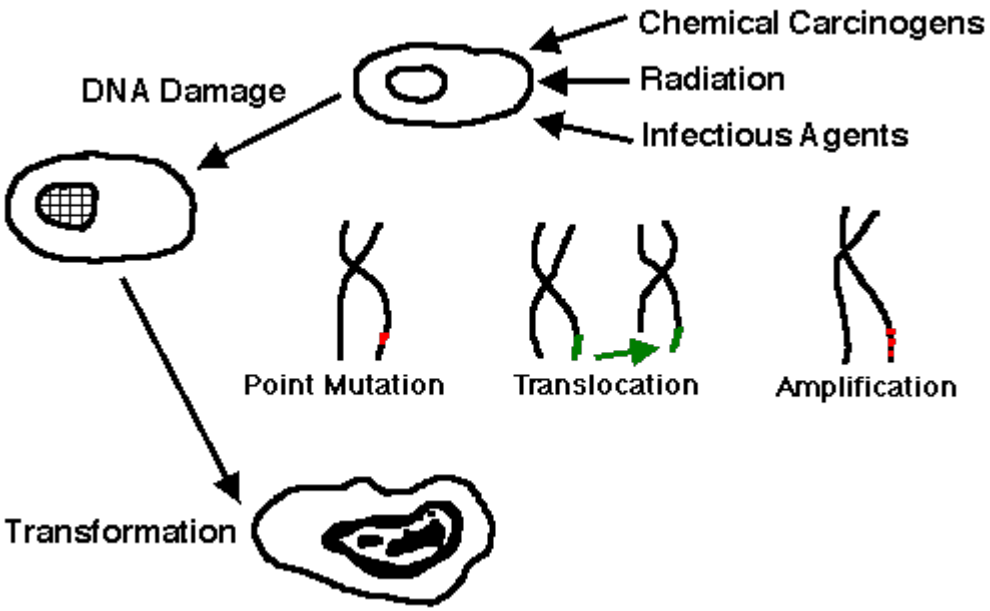
Clinical Vignette #3

- Mr. Jones returns after his biopsy to discuss the results and what the next steps would be.

Biology of Tumour Growth

- Four phases
  - Transformation: malignant change in cell
  - Growth
  - Local invasion
  - Metastases (distant spread)

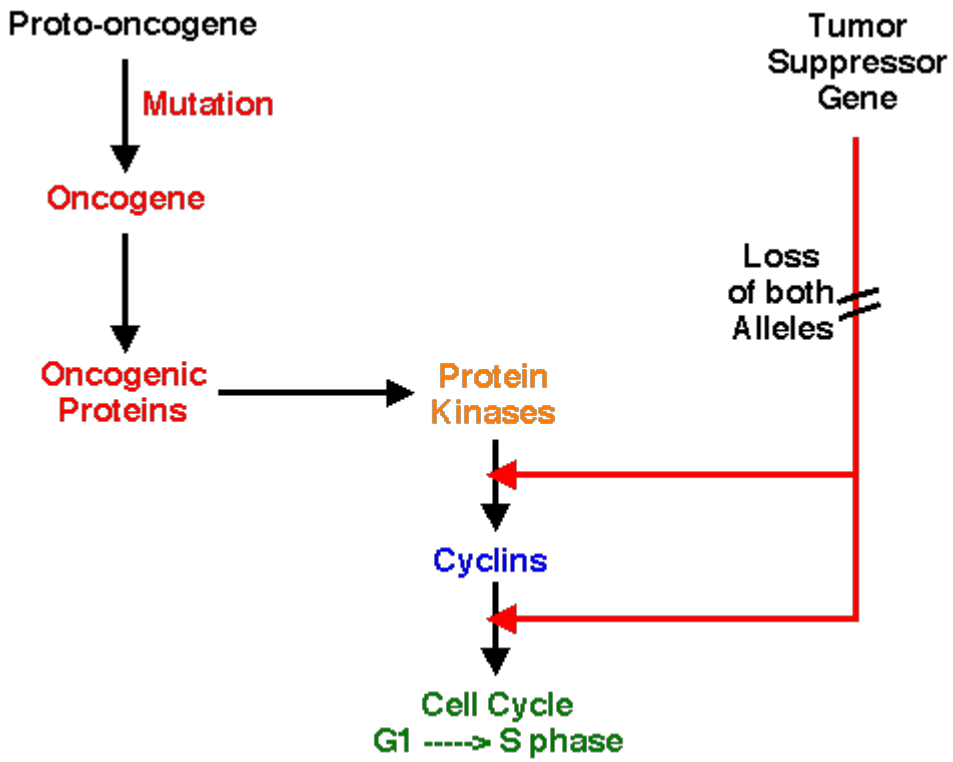
How it all starts
Transformation



Transformation

- Radiation Damage
  - UV exposure and melanoma
- Chemical Carcinogens
  - Benzene, nitrosamines
- Infectious agents (viruses)
  - EBV and nasopharyngeal carcinoma

Development of Cancer



Neoplasia, or uncontrolled cellular proliferation, can result either from mutations that "turn on" the oncogenes that stimulate growth, or from mutations that result in loss of tumor suppressor genes and their products that inhibit growth

Terminology

- Tumours have two major components
  - Parenchyma: proliferating neoplastic cells
  - Stroma: supporting tissue
- Parenchyma obviously important but growth/spread of tumour dependent on stroma also
- Nomenclature of tumours determined by the parenchymal component
- Treatment strategies aimed at both components

Terminology

- Suffix “oma” refers to benign tumours
- Classified from the organ where they originated
  - Lipoma: fat cell origin
  - Fiboma: fibrous tissue

- Adenoma: a benign tumour that forms glandular patterns

Terminology

- Carcinoma: cancers of epithelial origin
- Sarcoma: mesenchymal tumours (connective tissues, blood)
- Adenocarcinoma: carcinomas that form glandular patterns
- Squamous cancers: arising from squamous cells and making keratin

Benign or Malignant?

- Hallmarks of Cancer
  - Clonality
    - All the cells in a given tumour are the same genetically
  - Invasion and Metastasis
    - Cancers can invade beyond normal tissue boundaries and spread diffusely in the body

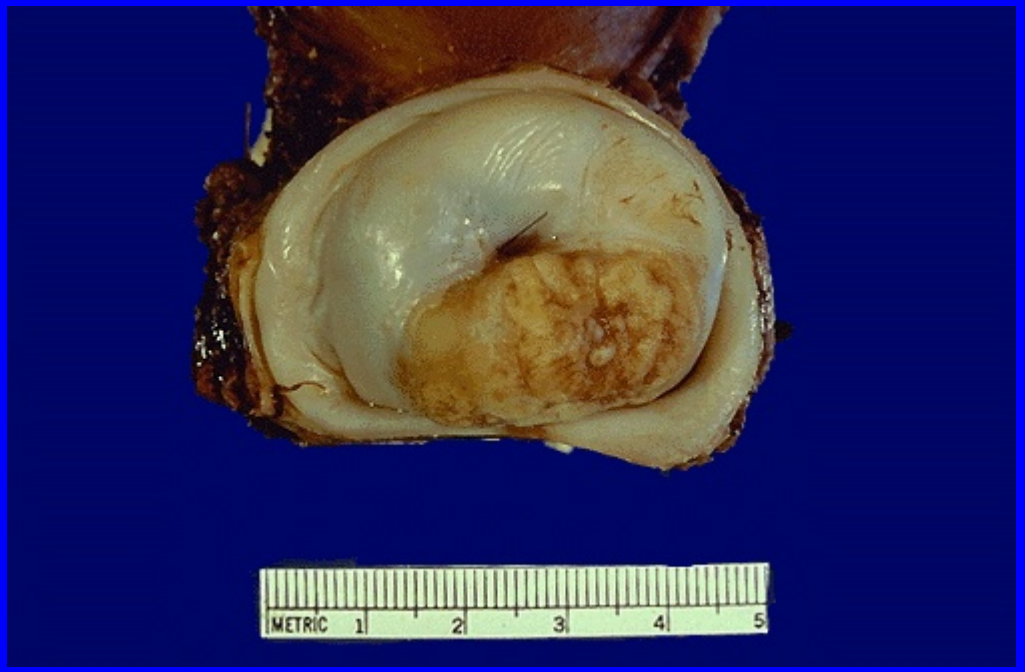
Staging and Grading

- After diagnosis is made, the cancer is graded and staged
- Grade: how aggressive is it
  - Well differentiated → anaplastic
  - More anaplastic = poorer prognosis
- Grading may help determine if extra treatment after surgery is needed
- Still a subjective area; pathologist dependent

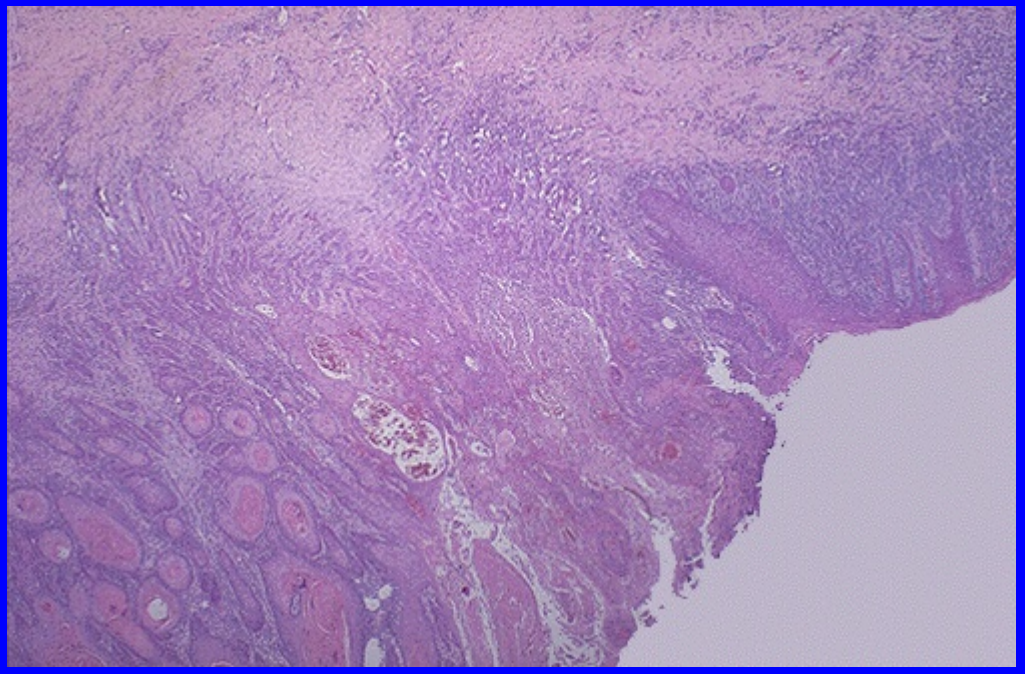
Staging and Grading

- Stage: How much cancer is there?
  - Local, locally advanced (nodes), distantly metastatic
  - Higher stage = poorer prognosis
- Staging systems give information on how to treat and prognosis
- Most cancers staged from I to IV

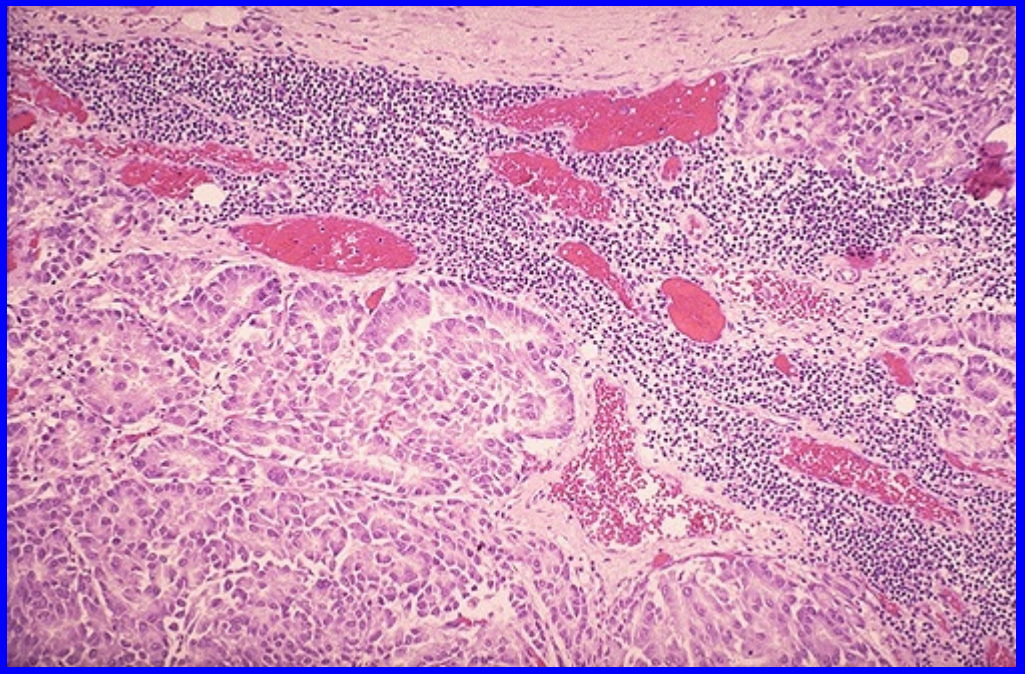
Carcinomas
Cervical cancer-Gross pathology



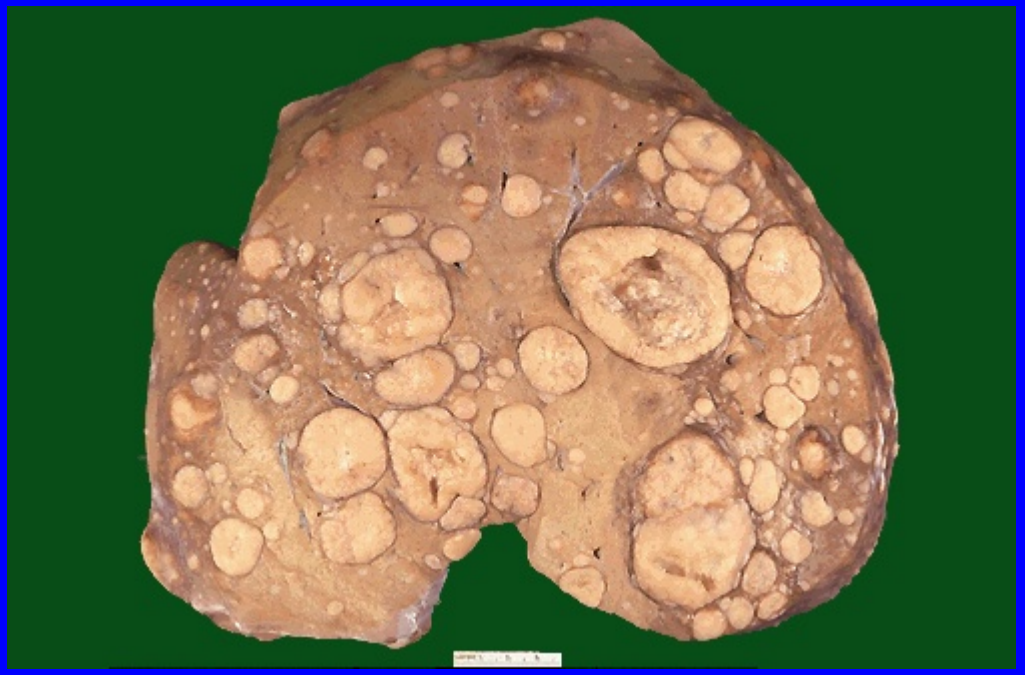
Local Invasion
Cervical cancer-microscopic



Metastases
Distant spread



Metastatic disease liver metastases



Treatment

Traditional paradigm of cancer treatment

Surgery

Radiation

Drugs (Chemotherapy)

Surgery

- Long considered the most important aspect of cancer treatment for solid tumours
- Controls the disease locally
- May be curative for many tumours especially if caught early
- Unfortunately, tumours often recur

Radiation Therapy

- Local therapy
- Causes DNA damage to cancer cells and leads to their death
- May be curative on its own
  - Cervical cancer
- May be given as an adjunct to surgery to improve cure/local control rates
  - Breast, rectal cancer
- More sophisticated techniques being developed to deliver RT with fewer side effects and more efficacy

Chemotherapy

- Multitude of drugs developed to kill cancer cells
  - DNA damage, RNA damage, inhibit cell growth and division, antimetabolites
- Damaging to normal cells also
  - Side effects of treatment
- Relatively non-specific
- Can be used as sole modality for cure (hematologic malignancies) or as adjunct to either surgery or radiation to cure
- May also be given to incurable individuals to palliate

Cancer Treatment

- New Paradigm
  - Get smart about the tumour
  - Don’t use non-specific treatments
- Small molecule oncology
  - Enzyme inhibitors, monoclonal antibodies
- Molecular profiling
  - Oncogenes, protooncogenes, apoptotic markers, cytogenetics

New Paradigm of Treatment

- Target unique proteins/genes/structures in cancer cells with novel agents
- Differential toxicity between the tumour cell and normal tissues
- More specificity for tumours makes cancer kill greater
- Combine newer treatments with traditional strategies

What about the stroma?

- To be lethal, cancers must spread and cause normal organs to fail
- Requires access to lymphatics and/or blood and travel to distant sites
  - Anti VEGF monoclonal antibodies
  - Antiangiogenic molecules, matrix metalloproteinase inhibitors in clinical trials
  - Much research in this area: more molecules to be developed
- Great opportunity for basic scientists and clinicians to collaborate

Clinical Vignette #4

- Now that surgery has been performed, Mr. Jones wants to know what, if anything, will happen now

General Principles

- Adjuvant Therapy
  - Any therapy given in conjunction with the main modality of treatment
    - E.g. chemo after surgery for breast cancer
  - Persistent microscopic tumour cells may have been left behind by the primary modality of treatment
  - Adjuvant treatment mops them up while still microscopic before they can regrow into incurable, metastatic disease

General Principles

- Metastatic Therapy
  - Treatment given in the metastatic setting
  - Usually cure isn't possible
    - Notable exceptions include testicular cancer, gestational trophoblastic neoplasia, Ewing's sarcoma
  - Goal is improving quality and quantity of life

Adjuvant Therapy

- Patients being offered adjuvant therapy may have **micrometastatic** disease
  - you can't see it on a scan
  - how do you know if the patient is benefiting?
  - Best given early post surgery or radiation so you are treating the least number of cancer cells
- Have to discuss the potential benefits of treatment
  - no guarantees
  - based on population statistics

Adjuvant Therapy Example

- A patient has stage II breast cancer
  - stats say that 60% of women will be cured with surgery
  - combination chemotherapy can improve the chances of survival by 25% (relative risk reduction of death)
- Question
  - Does that mean that every woman benefits from chemo?

Adjuvant Example

- Surgery Alone
- 60% cured
- 40% will die

- You have no idea up front who is cured and who will die

- Surgery + Chemo
- 70% cured
  - chemo adds 10%
- 30% will die

- You have no idea up front who is cured, who will die and who were the 10% that benefited

Adjuvant Chemo

- Bottom line is that we know statistically for the population there is a benefit to treat
- You never know which individual is going to benefit
  - you have to treat them all to give them the insurance policy
- molecular profiling may help in the future

Conclusions

- Cancer is a major health problem for Canadians and will get worse as we all age as a society
- Solid tumours go through a fairly predictable pattern from pre-cancerous to frankly malignant lesions
- The hallmark of cancer is that the cells are monoclonal and have the ability to invade and spread

Conclusions II

- We can intervene by improving
  - Detection
  - Treatment
  - Prevention
- Traditional treatment methods are still useful and have brought us a long way
  - Surgery, radiation, chemotherapy

Conclusions III

- The future of cancer research will be in “getting smart” about cancer
  - Tumour profiling
  - Small molecules
- Targeting the stroma (antiangiogenesis) may not kill tumours but prevent them from spreading
  - Coexist with a small amount of tumour
  - ?cancer as a chronic illness