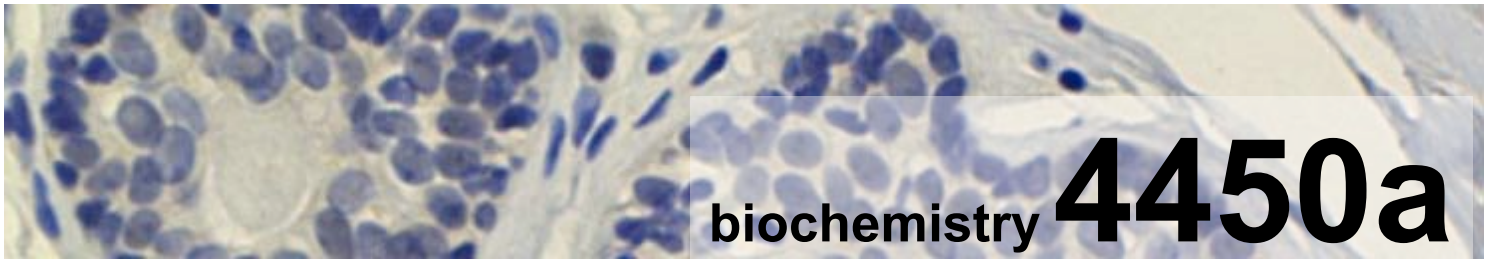
Lecture 1: Course Introduction and Cancer ‘by the Numbers’



Introduction

Rationale for this course

Course ‘Philosophy’

Course Outline

Evaluation

Themes

Critical Thinking

Cancer ‘by the numbers’

DAVID RODENHISER, PhD *(Course Coordinator)*

Associate Professor, Depts of Paediatrics, Biochemistry, Oncology; UWO
Principal Investigator, London Regional Cancer Centre
Scientist: Child Health Research Institute
drodenhi@uwo.ca *Room A4-134 Victoria Research Laboratories*

My lab focuses on the environmental role of epigenetics in the processes of gene expression, breast cancer and embryonic development.

FRED DICK, PhD

Assistant Professor, Depts of Biochemistry, Oncology; UWO
Principal Investigator, London Regional Cancer Centre
Scientist: Child Health Research Institute
fdick@uwo.ca *Room A4-136 Victoria Research Laboratories*

My lab's research is focused on the fundamental mechanisms that regulate the mammalian cell cycle and how they are disrupted in cancer.

CAROLINE SCHILD-POULTER, PhD

Assistant Professor, Dept of Biochemistry, UWO
Cell Biology Research Group, Robarts Research Institute
cschild-poulter@robarts.ca

My research program is centered on the study of the mechanisms implicated in the NHEJ DNA repair pathway.

4450A: Rationale for this course:

- Provide an introduction to the molecular genetic basis of human cancers.

- Recent breakthroughs in molecular genetics have lead to landmark advances in our understanding of the molecular causation and treatment of the multiple types of human Cancers.

- Cancer will be presented as a consequence of interactions between a cell's genetic blueprint and the external environment that alters that cell's selective advantage over its neighbours.

4450A: Course ‘Philosophy’ or Approach

An overview of ‘Cancer’

- as a disease process that is the ‘flipside’ of development
- many of the same genes, but inappropriately expressed or regulated

Cancer as a set of diseases that are:

- gene(s) specific and tissue(s) specific
- cell gains a selective advantage relative to its neighbours
- genes and epigenetic changes … mediated by the external environment

Molecular mechanisms that we know are contributing to Cancer

New approaches**:** revert altered cells to ‘normal’, or eliminating those cells.

4450A: Course ‘Philosophy’ or Approach

We will:

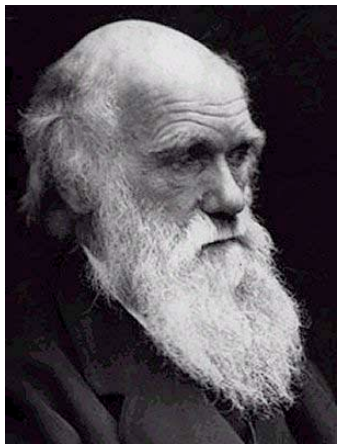
… investigate key cellular pathways that are frequently targeted and hijacked in tumour cells leading to neoplasia,

… discuss the mechanisms by which environmental factors affect tumour development

… discuss novel cancer models and molecular therapies.

Concepts … Pathways … Targeting

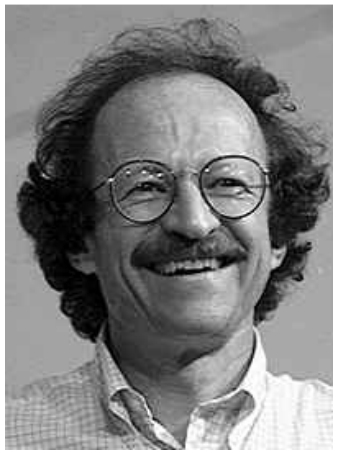
Cancer Research: a continuum from Labbench to Bedside



Darwin
Selective advantage

McClintock
transposons

Folkman
Angiogenesis



Varmus
oncogenes

Grissom
profiling

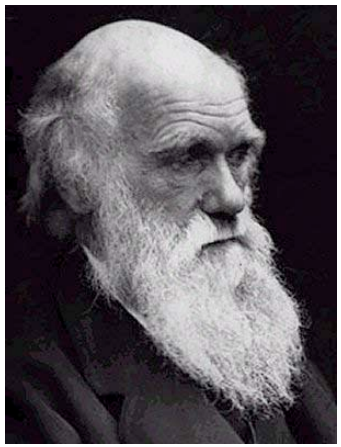
House
clinical

Basic Science

Translation

Clinical applications

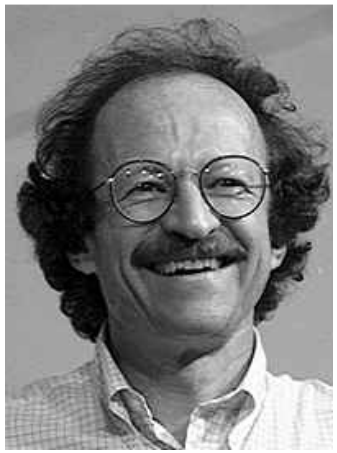
Cancer Research: a continuum from Labbench to Bedside



Darwin
Selective advantage

McClintock
transposons

Folkman
Angiogenesis



Varmus
oncogenes

Grissom
profiling

House
clinical

Basic Biology

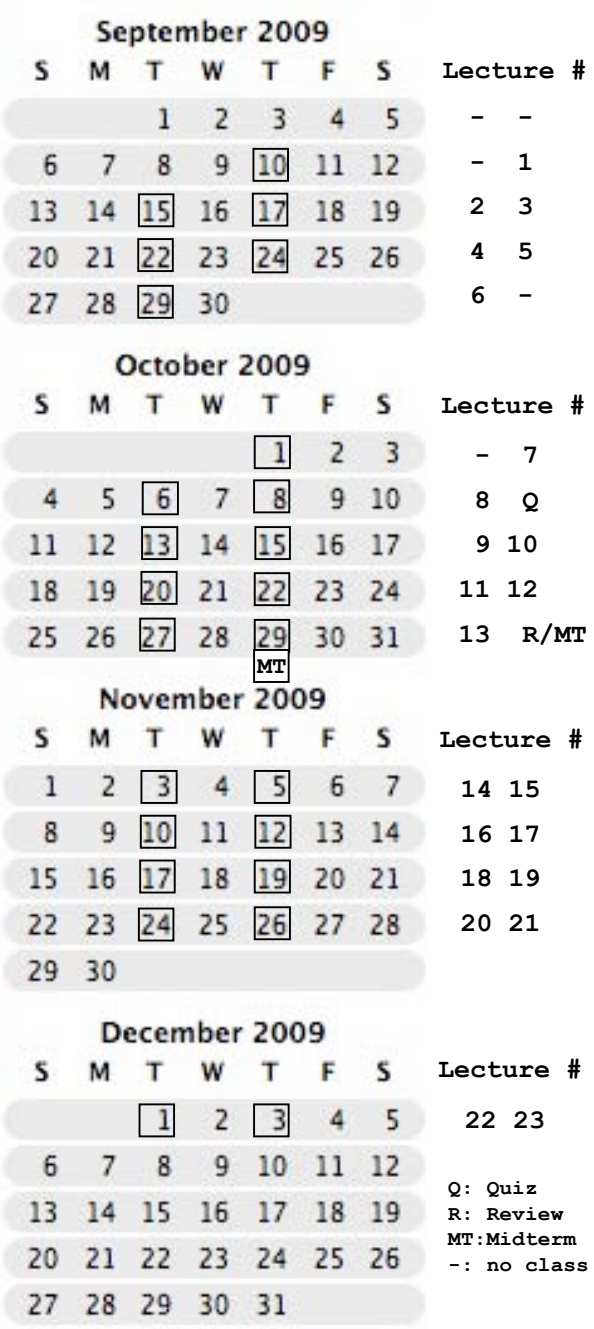
Early Diagnosis

Prognosis

Prediction

Treatment

Followup



Biochemistry 4450a Lecture Schedule (2009):

Tentative schedule: August 24, 2009

lecture 1: Course Introduction and Cancer 'by the Numbers'	**INTRODUCTION** (Dr Rodenhiser)
lecture 2: The Hallmarks of Cancer	
lecture 3: The 'Cancer Genes': Viral Oncogenes and Rb	**CONCEPTS** (Dr Dick)
lecture 4: The 'Cancer Genes': ras and p53	
lecture 5: Multistage Progression and the two hit (more or less) hypothesis	
lecture 6: Genomic Instability: enabling Cancer progression	
lecture 7: Immortality and Senescence	
lecture 8: Model organisms used in Cancer Biology	
Quiz … 50 minutes: October 8 (in class)	
lecture 9: Genome Integrity I: Apoptosis	**PATHWAYS** (Dr Schild-Poulter)
lecture 10: DNA Repair overview	
lecture 11: Nucleotide Excision Repair	
lecture 12: Colon Cancer	
lecture 13: Defects in the BRCA genes and Breast Cancer	
Review in class prior to midterm (optional)	
Midterm … 2 hours … tentative date: October 29th evening	
lecture 14: Gene-Environment interactions	
lecture 15: Epigenetics and Cancer: translating basic science to treatment	**TARGETING** (Dr Rodenhiser)
lecture 16: Metastasis and Angiogenesis	
lecture 17: Cancer Pharmacogenetics and Proteomics	
lecture 18: Molecular Diagnostics and Counselling	
lecture 19: Molecular Profiling of tumours: array technology	
lecture 20: New Cancer Therapies I: Antisense technologies	
lecture 21: New Cancer Therapies II: The concept of Viral therapies	
lecture 22: Targeting Cancer by Viral therapies: Reo	
lecture 23: Summing up, review; feedback	
Final exam … 3 hours … date to be determined	

http://publish.uwo.ca/~drodenhi/Biochem450A.html
http://webct.uwo.ca/

The 4450a website: http://publish.uwo.ca/~drodenhi/Biochem450A.html

Source for:

Updates and Information

General Course Information

- **Course Coordinator:** Dr. David Rodenhiser, PhD.
  Associate Professor (Paediatrics, Biochemistry and Oncology)
  Principal Investigator in the London Regional Cancer Program
  Scientist at the Children's Health Research Institute
  email: drodenhi@uwo.ca phone: 519.685.8600 X52198
- **Lecturer:** Dr. Fred Dick, PhD.
  Assistant Professor (Biochemistry, Paediatrics and Oncology)
  Principal Investigator in the London Regional Cancer Program
  Scientist at the Children's Health Research Institute
- **Lecturer:** Dr. Caroline Schild-Poulter, PhD.
  Assistant Professor (Biochemistry)
  Cell Biology Research Group, Robarts Research Institute

Course Teaching Assistant: TBA

email:

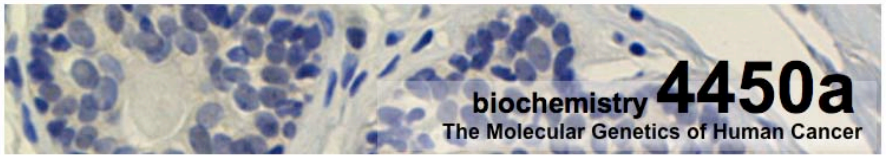
Western

Lectures: 10:30-11:30 on Tuesdays and Thursdays

Biological and Geological Sciences Building Room 1056

Click here to see the **2009 Tentative Lecture Schedule:** 4450Aschedule2009.pdf

Click here to see Lecture Notes and Papers webpage



Lecture Notes and Required Readings: 2009

These notes and papers are password protected, are in .pdf format and are for the personal use of UWO students enrolled in Biochemistry 4450A. Other reproduction of lecture notes is not permitted without permission from Dr. Rodenhiser. Published papers are copyrighted by the publishers and are provided for personal use only.

Tentative 2009 lecture schedule: 4450Aschedule2009.pdf

Click here to go back to General Course Information page

Lectures, Dates and Titles	Downloadable: Notes and Papers (available soon)
Lecture 1 (September 10) ... Course Introduction	4450A2008lect1.pdf
Lecture 2 (September 15) ... Hallmarks of Cancer	4450A2008lect2.pdf ; 02.Hanahan.pdf
Lecture 3 (September 17) ... Cancer Genes: Viral Oncs and Rb	notes 03 ; Sherr03.pdf
Lecture 4 (September 22) ... Cancer Genes: ras and p53	notes 04 ; Downward ; ElDeiry
Lecture 5 (September 24) ... Multistage Progression / 2 hit	notes 05 ; Knudson ; Pane ; Hahn
Lecture 6 (September 29) ... Genomic Instability	notes 06 ; Fodde ; Lengauer
Lecture 7 (October 1) ... Immortality and Senescence	notes 07 ; Masutomi ; Narita
Lecture 8 (October 6) ... Model Organisms	notes 08 ; Hariharan ; Vandyke

http://webct.uwo.ca is your source for:

Lecture notes: pdf format

Required Readings : pdf format

Evaluation, Expectations and Marking ‘Philosophy’:

Critical Thinking:

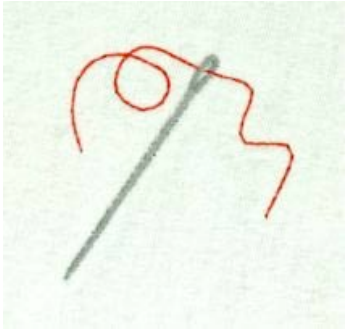
Synthesis and Coordination of thoughts and ideas

Assembling facts into systems having complex inter-relationships

How do these ‘threads’ tie together the concepts

What was the most important point presented?

What concept was the most difficult to understand?



Evaluation, Expectations and Marking ‘Philosophy’:

Evaluation

Quiz 10%

Midterm 30%

Final 60%

Short answer and Essay

Provide facts and relate to question asked

Narrative …tell a story

Organize your answer before you start writing

Western

Name and student number: _____

Biochemistry 450A FINAL

December 14, 2007

Answer both questions. Be sure to read the questions thoroughly and answer the questions directly and completely. Plan your time accordingly … you have 3 hours.

Question 1: Answer in the exam booklet (40 points).

Background: You are a 4th year student working on your honours project. Yesterday, at your weekly lab meeting, your supervisor Dr. Knowitall presented a new paper* published in Nature Genetics by a research group from Columbia University. This group looked at a number of very aggressive breast tumours from a number of women with hereditary mutations in BRCA1. They found that in addition to a BRCA1 mutation, many of the tumours also had alterations in the PTEN gene. PTEN acts as a tumour suppressor gene by negatively regulating the AKT/PI3K signaling pathway, which is upregulated and overactive in a variety of cancers. Suprisingly, many of the PTEN mutations they found were not small point mutations, but instead were large alterations involving chromosome breaks, inversions and deletions. In your lab meeting, the excitement is high as ideas for a new breast cancer therapy are discussed, based on these data. With the above information and with your knowledge from Biochem 450A, answer the following questions:

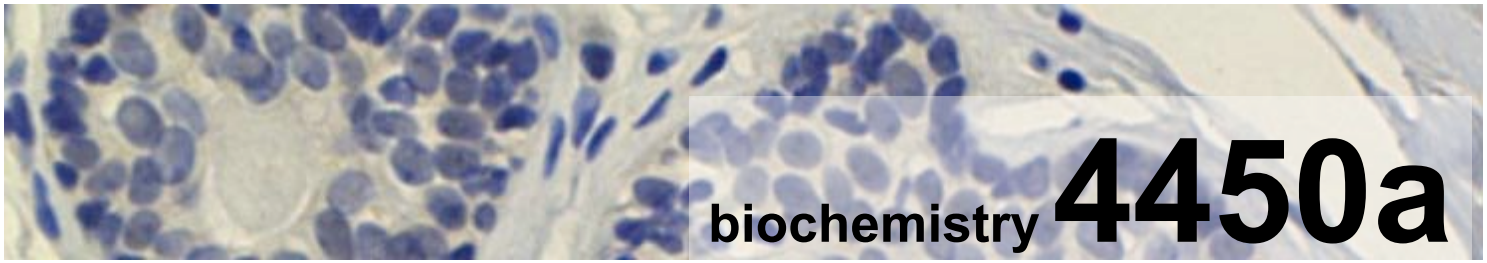
(a) What are the general features of a gene target that you need to consider when you create an ideal anticancer therapy? (You should be able to identify 5 or 6 such features).

(b) Dr. Knowitall points out that these PTEN negative breast tumours are also negative for estrogen receptor (ER) and Her2 receptor expression. One of the keener graduate students suggests that these would be great targets for antisense experiments. Describe antisense or similar knock down technology. How is it useful and when is it appropriate? What is your opinion of that graduate student's suggestion? Explain your reasons.

Answer **Question 2** in the **spaces provided on the attached pages (20 points).**

Answer 4 of the following 6 questions. For each of the following statements tell me if they are True or False and defend your answer in no more than the half page of space provided. Some of these can be answered either way, so the key to your answer is how well you argue your point of view. Each question is worth 5 points (1 for T or F, 4 for explanation).

1) "Transformation" of a normal cell into a cancer cell is the same as immortalization.



Recurring themes in this course:

Multistep progression

Genomic Instability

Selective Advantage

Regulatory circuits and ‘nodes’

Ask yourself:

How do the molecular pathways fit into these categories?

Critical Analysis of Cancer Research …

What is the Context of the Research? ….. What is the Hypothesis?

What were the Research Questions / Objectives?	What was asked?
What was the Experimental Design?	What did they do?
What did they discover?	What did they find?
How does this Research impact on the field?	What does it mean?

Cancer by the numbers

General cancer facts – Canada ….(www.cancer.ca)

Cancer is the leading cause of premature death (30% of potential years lost)

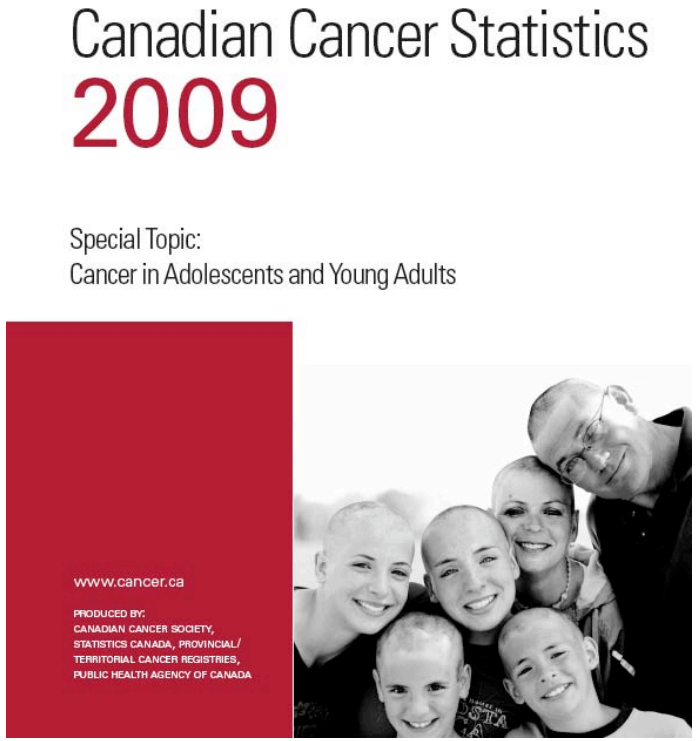
An estimated 171,000 new cases of cancer and 75,300 deaths from cancer will occur in Canada in 2009.

3,200 Canadians diagnosed each week

On the basis of current incidence rates, 40% of Canadian women and 45% of men will develop cancer during their lifetimes.

~1 in 4 Canadians will die of cancer in their lifetimes

(24% women; 29% men)



Cancer is primarily a disease of older Canadians ...

- Increased number of new cases of cancer is primarily due to an increasingly older population.

- 42% of new cancer cases and 60% of deaths due to cancer occur among people > 70 years old.

- Cancer incidence is rising in young women ages 20-39 (breast).

- For all cancers combined, 5 year survival increased from 80% (‘92 to ‘95) to 85% (‘01 to ‘04)

- Cancer rate is children in constant since 1985; death rates have declined

- 80% of children with cancer are either enrolled in a clinical trial or have been treated by a protocol established by a clincial trial.

Table 1.1

Estimated New Cases and Deaths for Cancers by Sex, Canada, 2009

	New Cases 2009 Estimates			Deaths 2009 Estimates		
	Total*	M	F	Total*	M	F
All Cancers	**171,000**	**89,300**	**81,700**	**75,300**	**39,600**	**35,700**
Prostate	25,500	25,500	–	4,400	4,400	–
Lung†	23,400	12,800	10,700	20,500	11,200	9,400
Breast	22,900	180	22,700	5,400	50	5,400
Colorectal	22,000	12,100	9,900	9,100	4,900	4,200
Non-Hodgkin Lymphoma	7,200	3,900	3,300	3,200	1,750	1,450
Bladder†	6,900	5,100	1,750	1,850	1,300	550
Melanoma	5,000	2,700	2,300	940	580	360
Thyroid	4,700	990	3,700	190	70	120
Leukemia†	4,700	2,700	1,950	2,500	1,450	1,050
Kidney†	4,600	2,800	1,800	1,600	1,000	610
Body of Uterus	4,400	–	4,400	800	–	800
Pancreas	3,900	1,900	2,000	3,900	1,850	2,000
Oral	3,400	2,200	1,150	1,150	770	390
Stomach	2,900	1,850	1,050	1,850	1,150	720
Brain	2,600	1,450	1,150	1,750	1,000	750
Ovary	2,500	–	2,500	1,750	–	1,750

(Canadian Cancer Society, 2009)

Three cancer types account for ~55% of the new cases:

Males: prostate, lung (28%), and colorectal cancers
Females: breast, lung (26%), and colorectal cancers

Lung Cancer: leading cause of premature death due to cancer
~1/3 of cancer deaths in men and 1/4 in women.
(and it's preventable!!!)

In women: Since 1979 lung cancer cases have tripled (!) … levelling off.

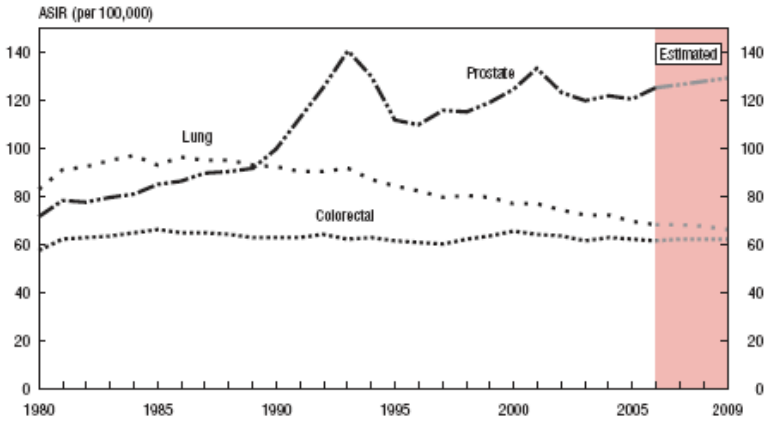
Among men, prostate cancer is the most commonly diagnosed cancer, but lung cancer is the leading cause of death.

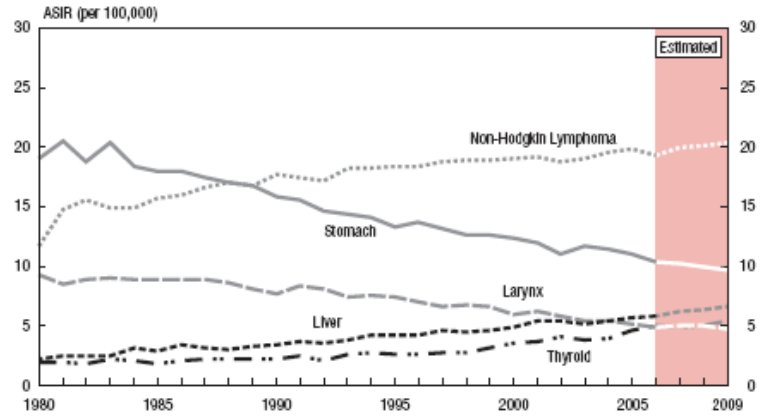
- Lung cancer rates leveled off in the mid-1980s and have since consistently declined, (reflecting a drop in tobacco consumption beginning in the mid-1960s).

males

Age-Standardized Incidence Rates (ASIR) for Selected* Cancers, Males, Canada, 1980-2009

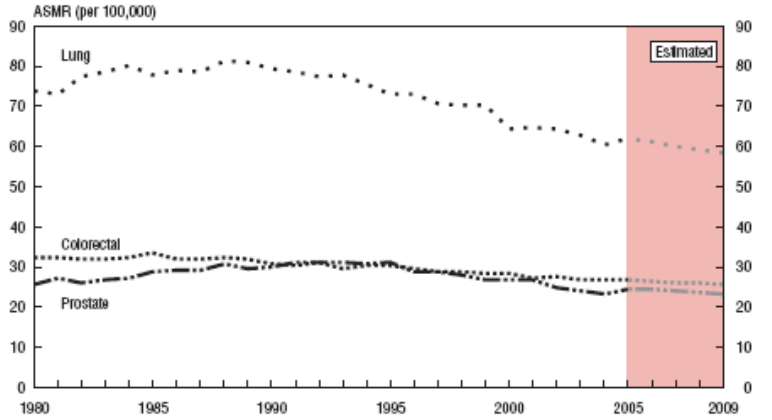
incidence

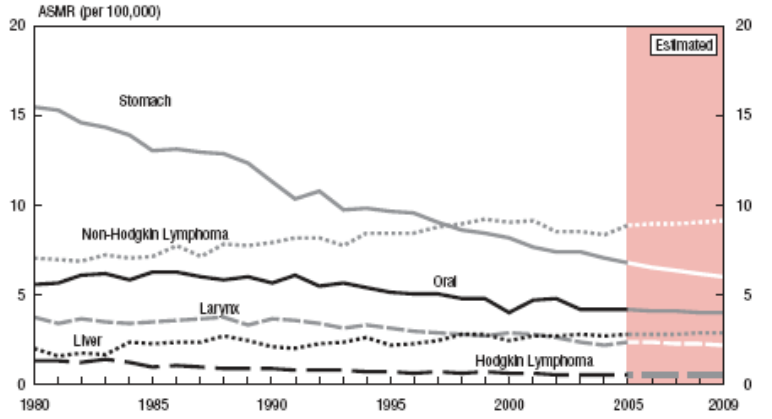




Age-Standardized Mortality Rates (ASMR) for Selected* Cancers, Males, Canada, 1980-2009

mortality

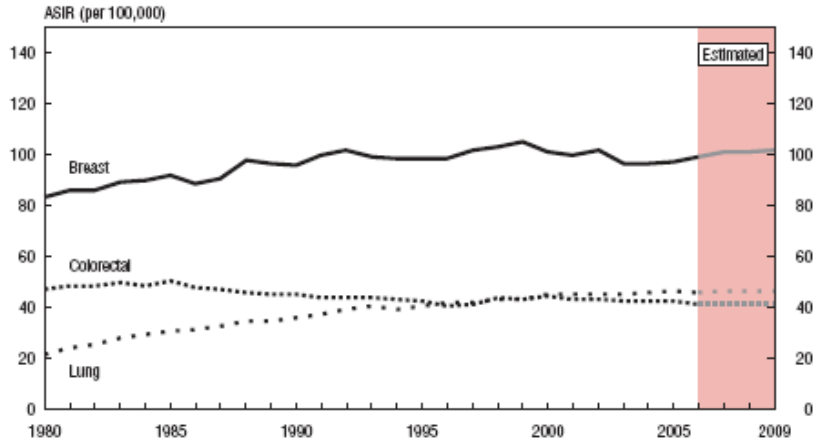




females

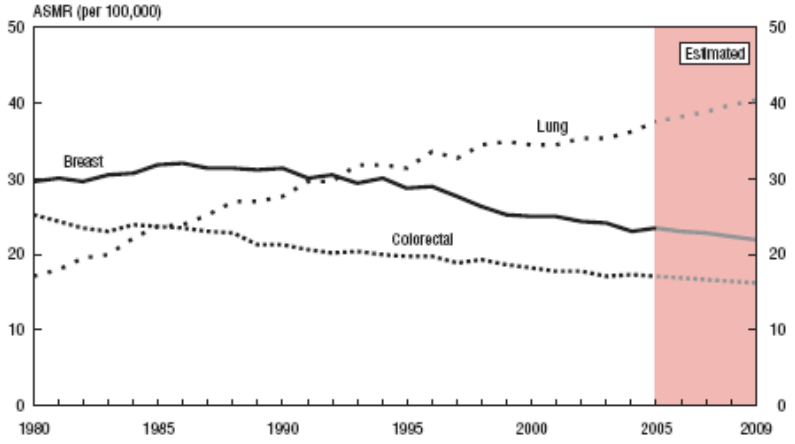
Age-Standardized Incidence Rates (ASIR) for Selected* Cancers, Females, Canada, 1980-2009

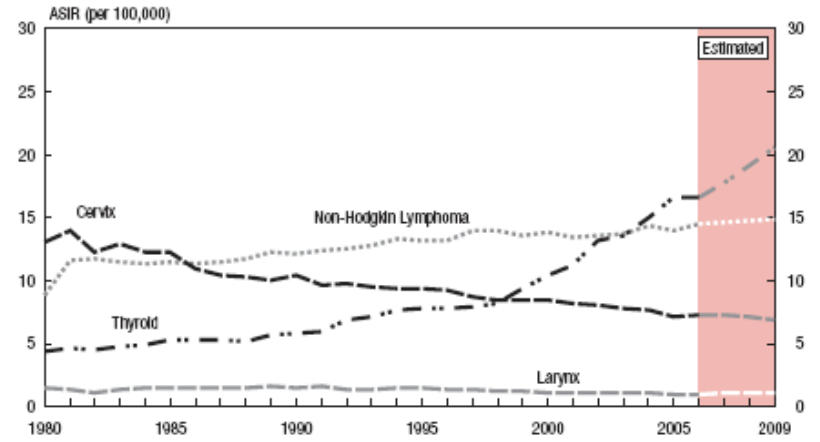
incidence

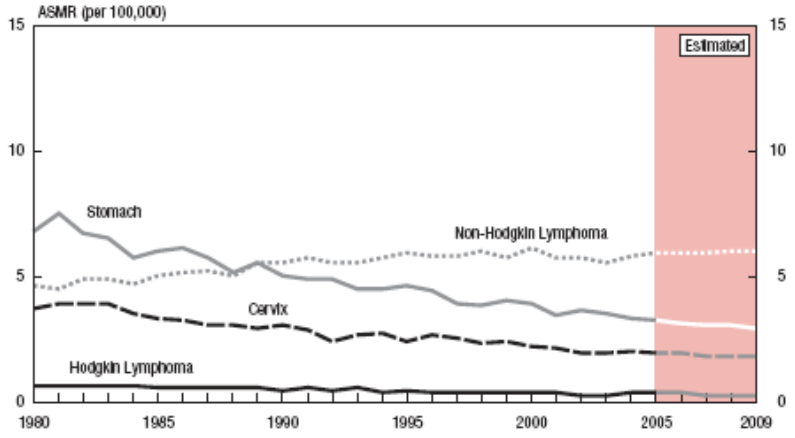


Age-Standardized Mortality Rates (ASMR) for Selected* Cancers, Females, Canada, 1980-2009

mortality







Breast Cancer:

- incidence among women over 50 rose steadily, but gradually, between 1980s and 1990s (likely due to use of mammography, tendency to delay having kids and declines in hormone replacement therapy).

- female breast cancer mortality rates have declined steadily since mid-'80s; about 2% decdrease per year (~30% total decrease).

- The breast cancer mortality rate is at its lowest since 1950.

- There is evidence for improved survival due to both organized mammography screening and adjuvant therapies following breast cancer surgery.

…. Early diagnosis! …. *(cancer progression model)*

Estimated Five-Year Relative Survival Ratio (%) (95% Confidence Interval) for Selected Cancers by Sex, Canada (Excluding Quebec*), 2002-2004

	Relative Survival Ratio (%) (95% Confidence Interval)		
	Both Sexes	Males	Females
All Cancers	**62** (62-62)	**61** (61-61)	**63** (62-63)
Thyroid	98 (97-98)	94 (92-96)	99 (98-99)
Testis	–	96 (94-97)	–
Prostate	–	95 (95-96)	–
Melanoma	89 (88-90)	86 (85-87)	93 (91-94)
Breast	87 (87-88)	84 (78-90)	87 (87-88)
Hodgkin Lymphoma	86 (84-88)	85 (83-87)	87 (85-90)
Body of Uterus	–	–	85 (84-86)
Bladder†	77 (76-78)	78 (76-79)	75 (72-77)
Cervix	–	–	75 (73-76)
Kidney	66 (64-67)	65 (63-67)	67 (65-69)
Larynx	65 (63-68)	66 (63-69)	61 (56-67)
Oral	63 (62-65)	62 (60-64)	66 (63-68)
Colorectal	62 (61-62)	61 (61-62)	62 (62-63)
Non-Hodgkin Lymphoma	61 (60-62)	60 (58-61)	63 (62-65)
Leukemia	51 (50-52)	51 (50-53)	51 (49-53)
Ovary	–	–	40 (39-42)
Multiple Myeloma	34 (32-36)	34 (32-36)	34 (31-36)
Stomach	23 (21-24)	22 (20-23)	24 (22-26)
Brain	22 (21-24)	22 (20-23)	24 (22-26)
Liver	18 (16-19)	18 (16-20)	16 (13-19)
Lung	15 (15-15)	13 (12-13)	17 (17-18)
Esophagus	14 (12-15)	14 (12-15)	13 (11-16)
Pancreas	6 (5-6)	6 (5-7)	6 (5-7)

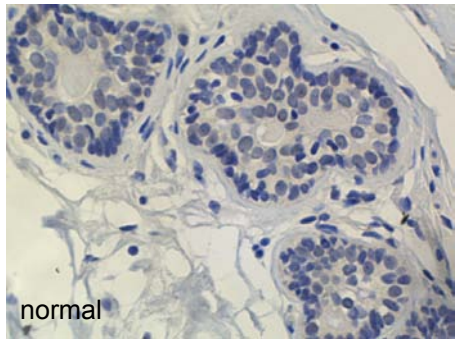
Complex relationships between:

Cancer type,
Exposures
Demographics
and
Treatment

What is the molecular basis for these various cancers?

What are the …

‘Rules that govern the transformation of normal cells into malignant cancer….’



Normal breast and tumour immunostained for DNMT3b. Butcher and Rodenhiser *(submitted to Cancer Research)*

The Hallmarks of Cancer

(Hanahan and Weinberg (2000); Cell 100: 57-70)

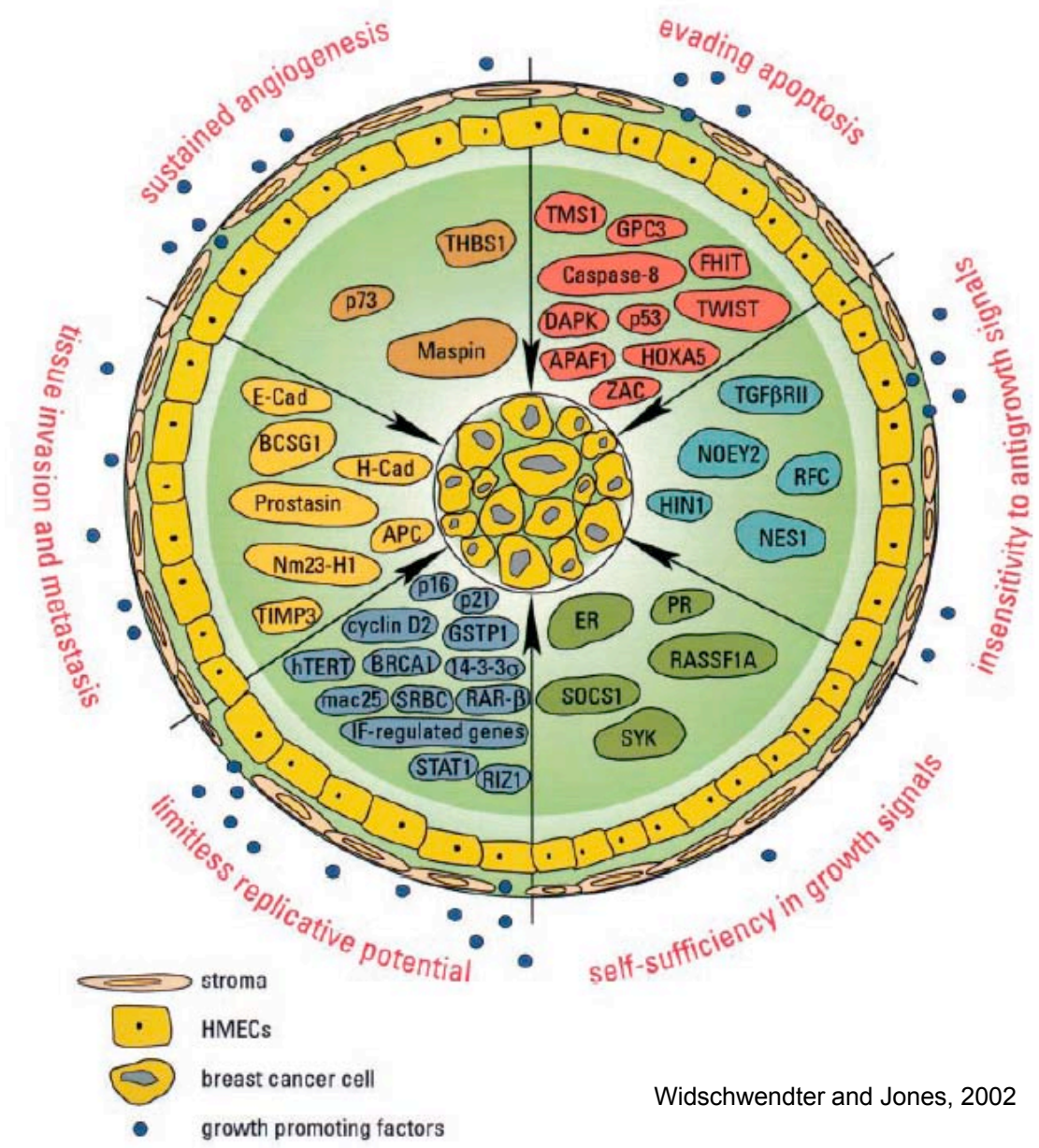
Six essential alterations that dictate malignant growth:

1. Self sufficiency in growth signals
2. Insensitivity to ‘anti-growth’ signals
3. Evasion of apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Tissue invasion and metastasis

Enabling characteristic: Genomic Instability

For example …
the BREAST CANCER perspective

alterations in cell physiology that define malignant growth:



Widschwendter and Jones, 2002