Learning objectives from the flipped videos

LO1: Able to explain how uncontrolled cell division can result in cancer, and identify causative factors (e.g. genetic, chemical carcinogens, radiation and loss of immunity) can increase the chances of cancer growth. (Flipped video)

LO2: Cancer develops by accumulation of mutations (taught in Cohort Class 1)

LO3: Properties of cancer cells (Flipped video)

RECAP from flipped videos:

LO1: Able to explain how uncontrolled cell division can result in cancer, and identify causative factors (e.g. genetic, chemical carcinogens, radiation and loss of immunity) can increase the chances of cancer growth.

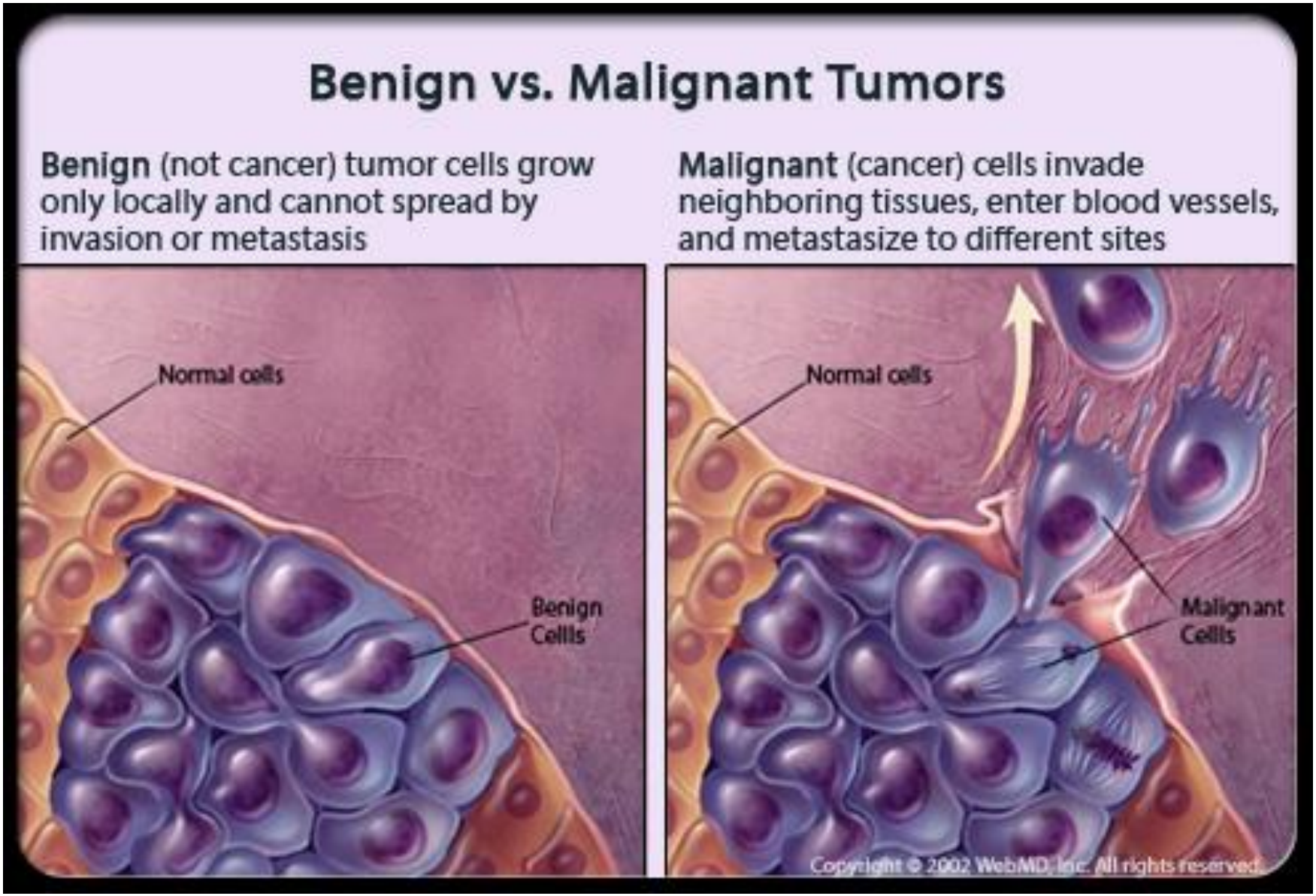
2 main properties of cancer cells

1) They proliferate in defiance of the normal constraints

- A condition of **uncontrolled proliferation** of cells. It is a disorder of the body's growth in which the cell **fails to respond** to normal controls on their multiplication and enlargement.

2) Invade and colonize territories normally reserved for other cells

- Cells, which should not be dividing at all, begin to undergo repetitive and very rapid cell cycles, forming tumours.


Benign vs. Malignant Tumors
Benign (not cancer) tumor cells grow only locally and cannot spread by invasion or metastasis
Malignant (cancer) cells invade neighboring tissues, enter blood vessels, and metastasize to different sites
Normal cells
Benign Cells
Normal cells
Malignant Cells
Copyright © 2002 WebMD, Inc. All rights reserved.

RECAP

RECAP from flipped videos:

LO3: 6 Properties of cancer cells

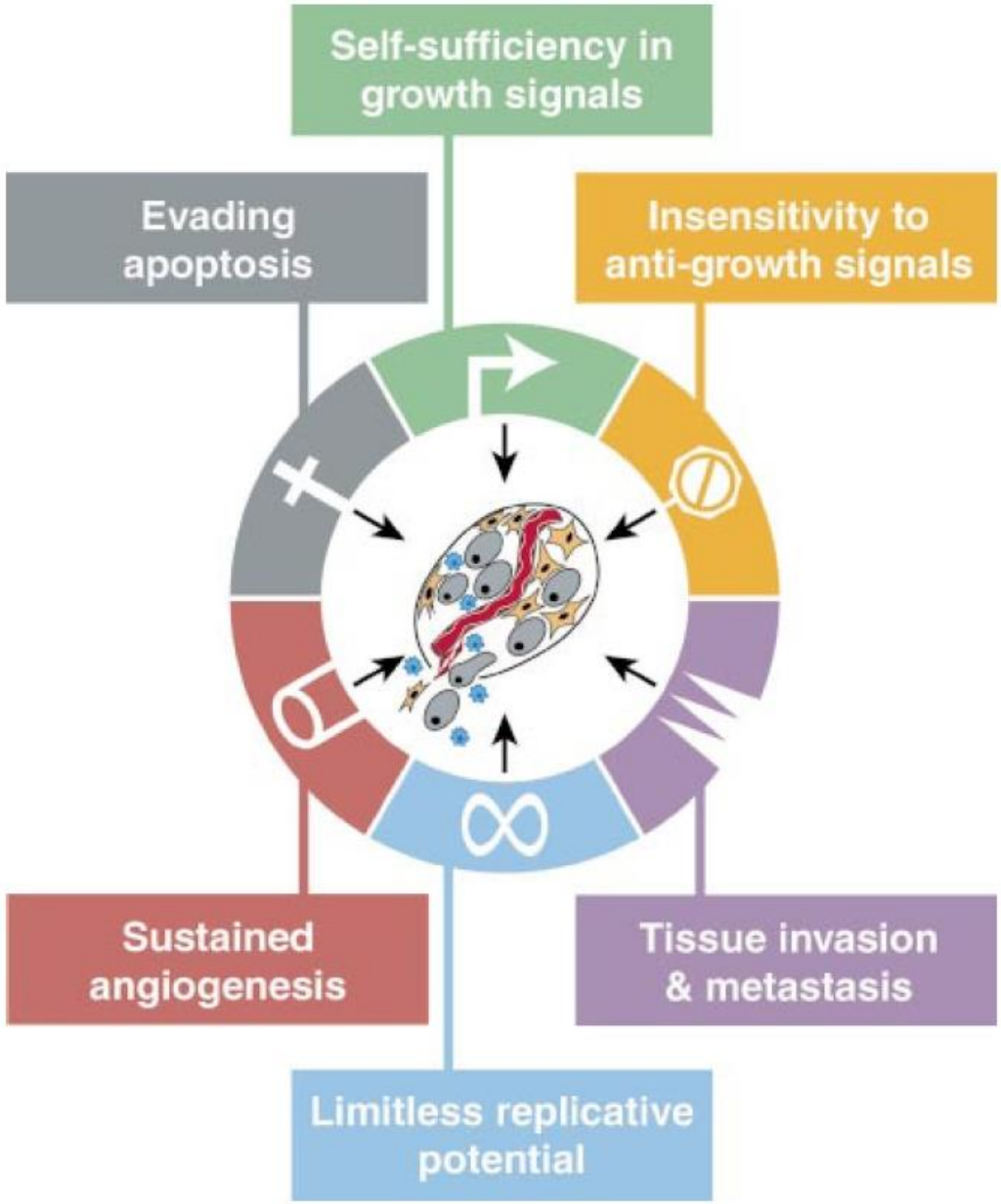
Normal versus tumour cells

RECAP

	Normal	Tumour
Cell division (growth factor dependent)	Dependent	Independent
Response to anti-growth signals	Cells stop dividing	Cells continues dividing
Response to genetic or environmental insults	Undergo apoptosis	Do not undergo apoptosis
Chromosome ends (telomeres; telomerase extends) after cell division	Shorter each time with cell division, telomerase inactive (except in gametes)	Telomerase is active. Maintain telomere length.
Stimulation of angiogenesis	NO	YES
Ability to invade and metastasize to other tissues	NO	YES

Upset of normal cell cycle regulation ➔ CANCER

6 main features of tumour cells



Week 13

CC1: 2 possible causes of cancer
(Lack of cell cycle controls and Genetics)

10.012 Introduction to Biology
17th and 18th Apr 2017

Reading list:
Campbell Biology (9th edition):
Chapter 18: pages 419-423 (Regulation of gene expression)
Essential cell biology (4th Edition): pages 712-724

Journal articles uploaded on eDimension

SINGAPORE UNIVERSITY OF TECHNOLOGY AND DESIGN
Established in collaboration with MIT

Overview of CC1 (week 13)

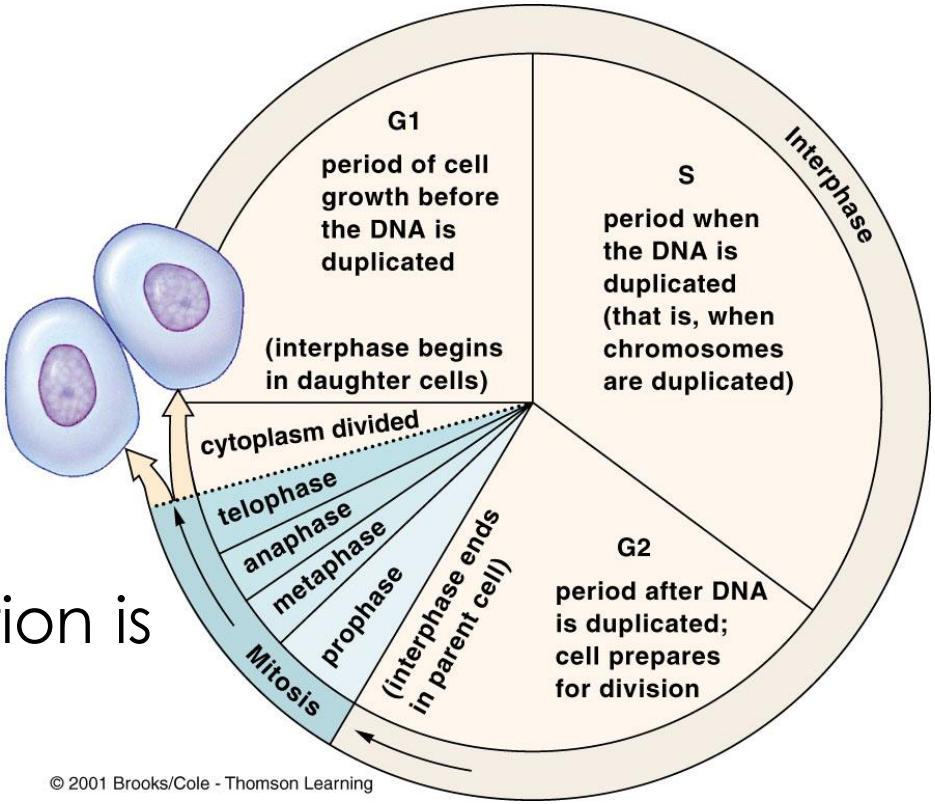
- Quiz
- Recap of flip lecture

2 possible causes of cancer:

- Genes that **control the progression of cell cycle** are mutated and are not able to function properly: Tumour Suppressor genes and Proto-Oncogene (Accompanying worksheet)

- Cancers that are **inherited (genetics and cancer)**

➔ case study using p53 inheritance



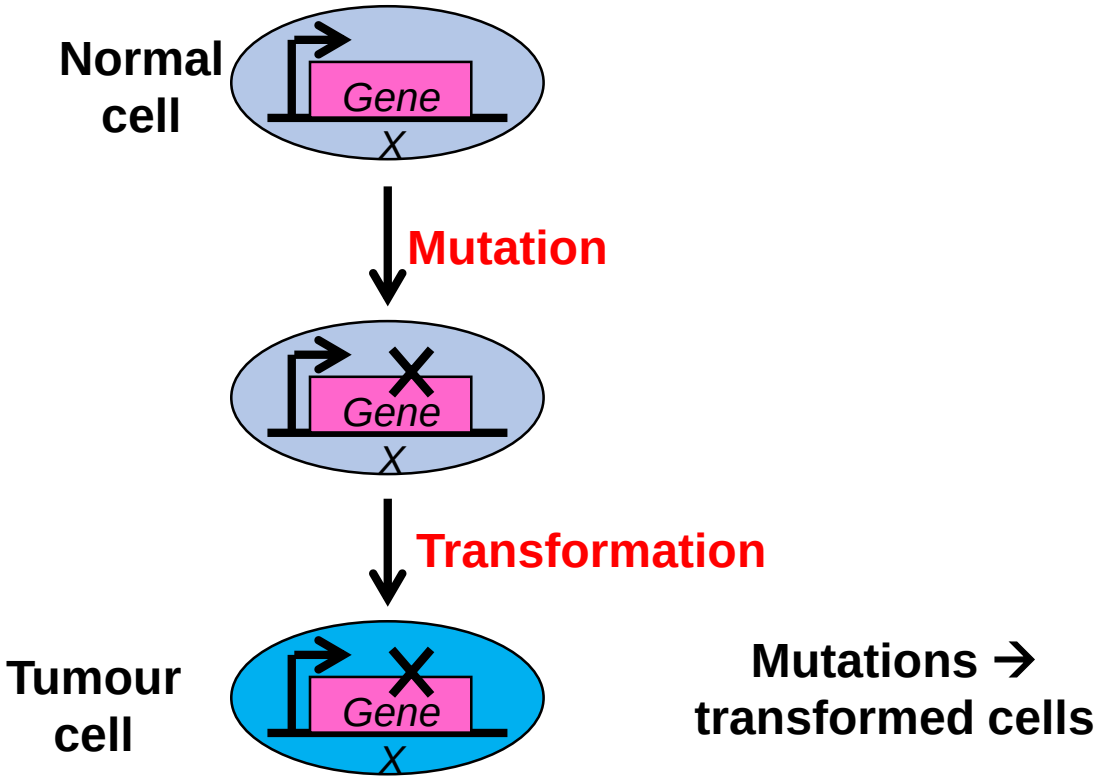
In normal cells: G1→ S transition is tightly regulated, focus on 2 groups.

- Cell cycle stimulating pathway (e.g. Ras) → **Proto-oncogene**

- Cell cycle inhibiting pathway (e.g. p53) →**Tumour suppressor genes**

Normal cells contain genes which when mutated may transform a cell into a tumor cell

Transformation: conversion of a normal cell to a cancerous cell



ONCOGENES

Proto-oncogenes (gas pedal)

These genes normally produce protein products that **stimulate cell division** in a normal cell.

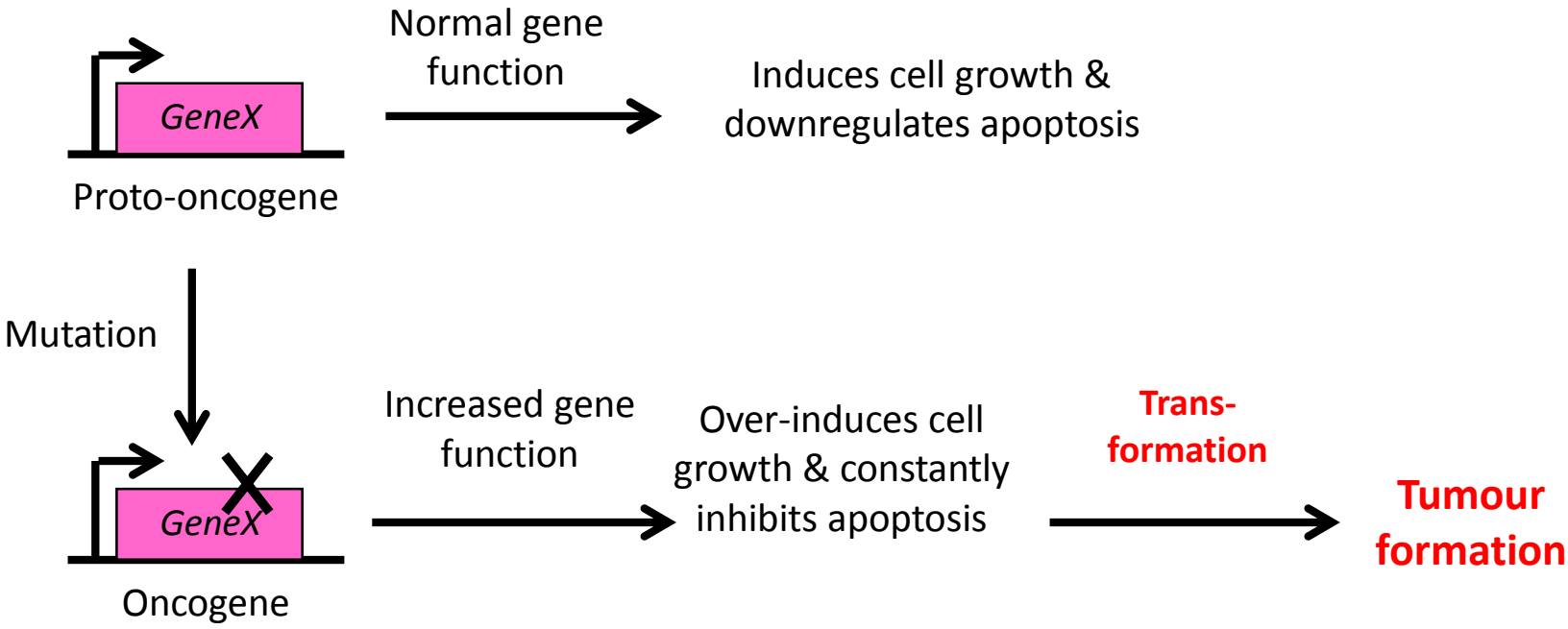
Oncogenes ⬆⬆

The mutated forms of proto-oncogenes stimulate mitosis **even though normal growth signals are absent.** (independent activation)

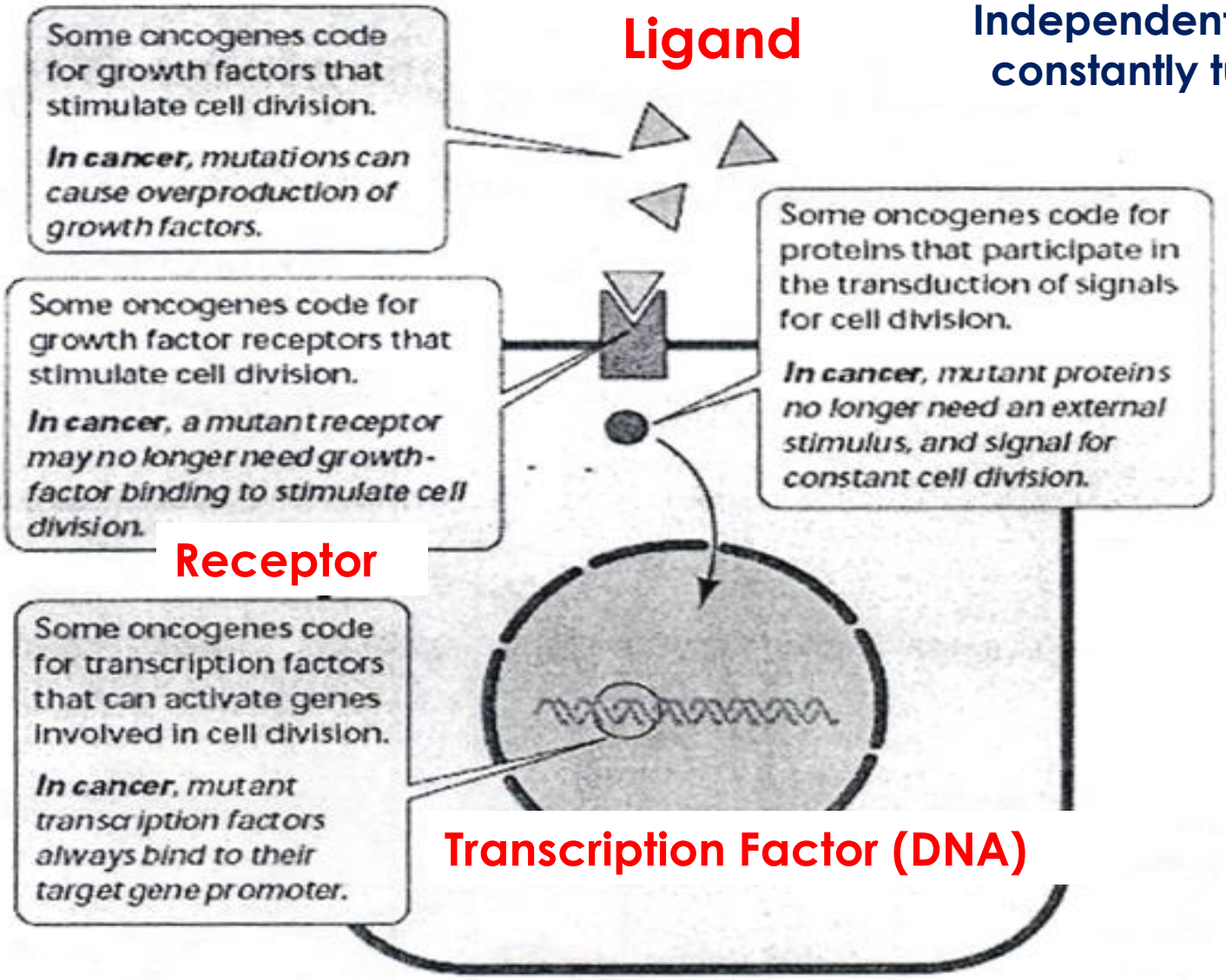
E.g. Ras protein.

Oncogenes:

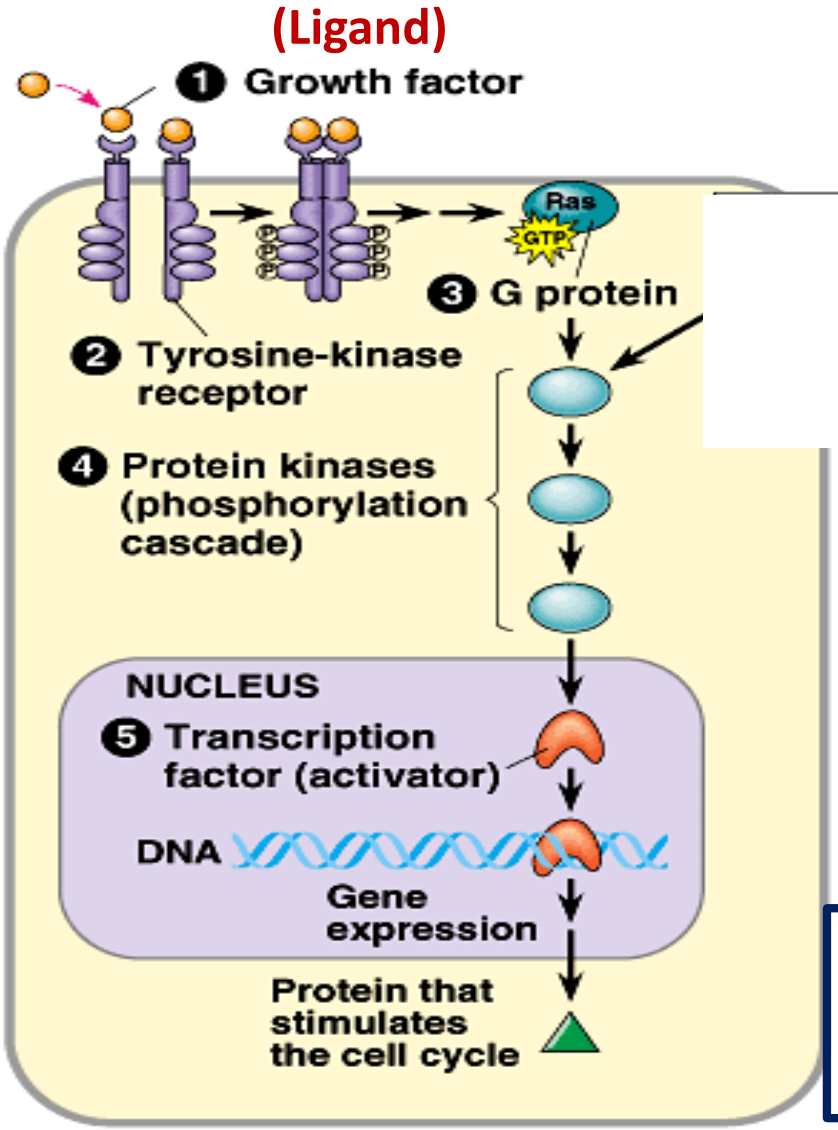
Usually **dominant** and **gain-of-function** mutations
One copy of mutated gene for phenotype to appear.



Proto-oncogene mutation at every levels



Ras: as an example of a proto-oncogene



Cell cycle stimulating pathway

With a mutation in Ras or other components of the pathway, excessive cell division and cancer may result

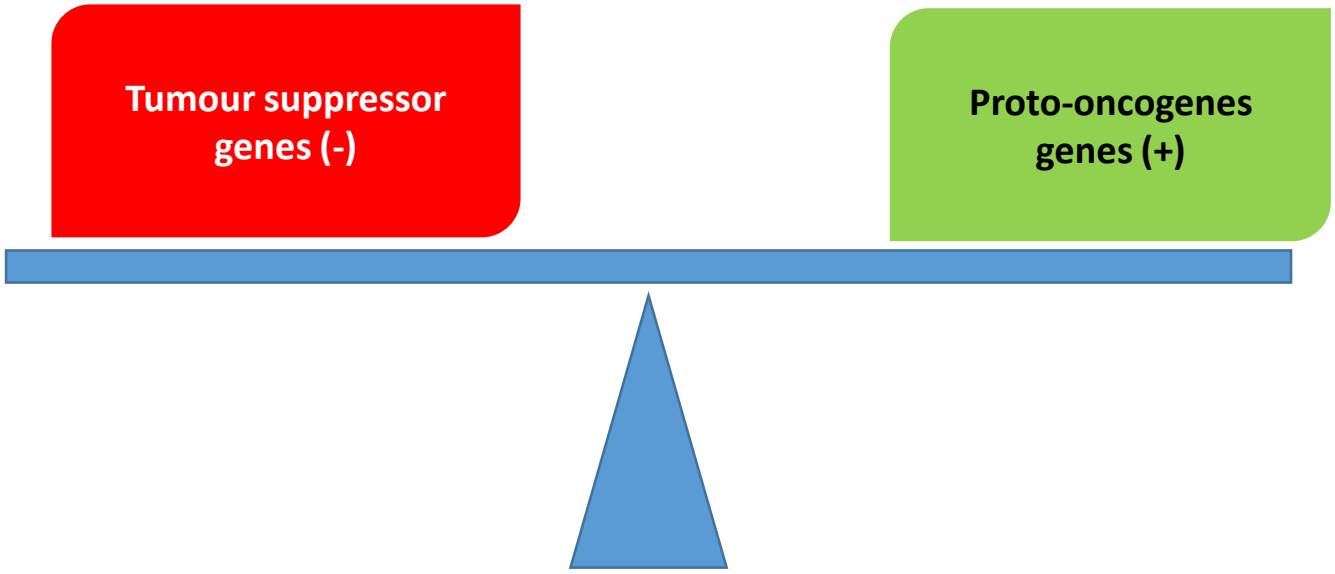
Normal Ras
WITH ligand (GF)= ON
WITHOUT ligand (GF)= OFF
=> regulated cell growth

Mutated Ras
WITHOUT ligand (GF)= ON
=> uncontrolled cell growth

Tumour suppressor genes (brakes)

Normally **inhibit cell division** in a normal cell to prevent inappropriate growth.

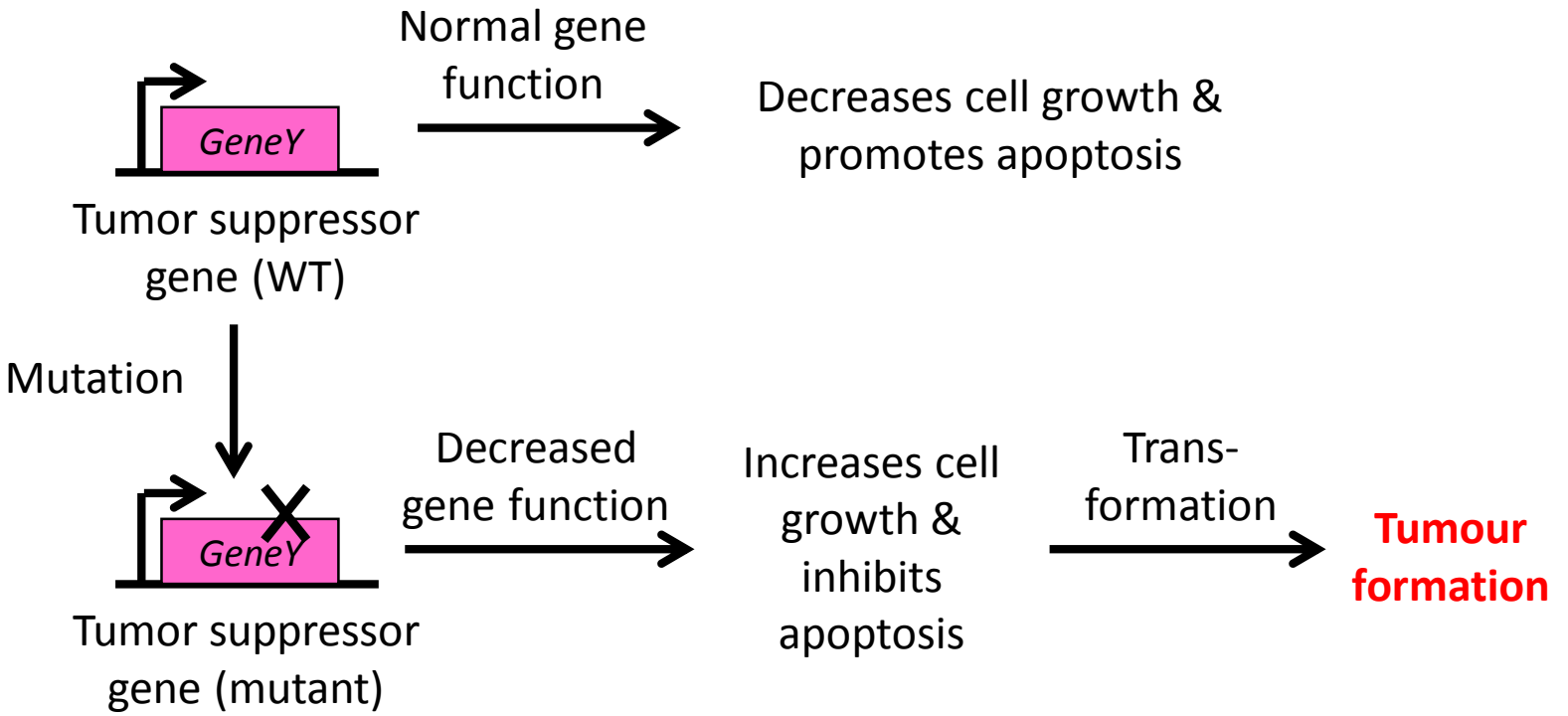
Mutation of these genes leads to **absence of suppression**. E.g. p53 protein



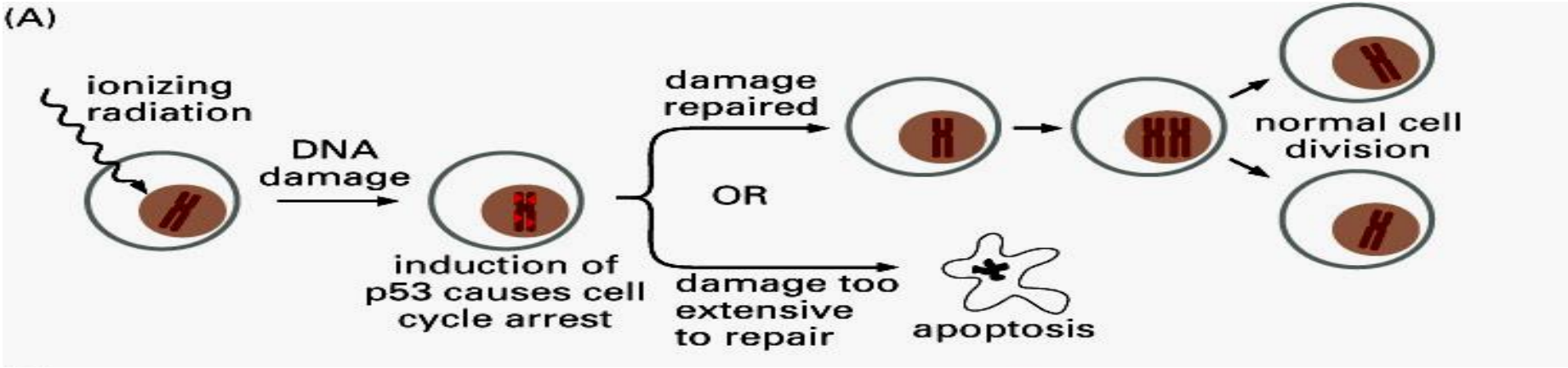
Tumor suppressor genes

Mutated tumor suppressor genes can transform cells into tumor cells

- Usually recessive **loss-of-function** mutations
- **2 copies** of the genes need to be mutated for a phenotype.

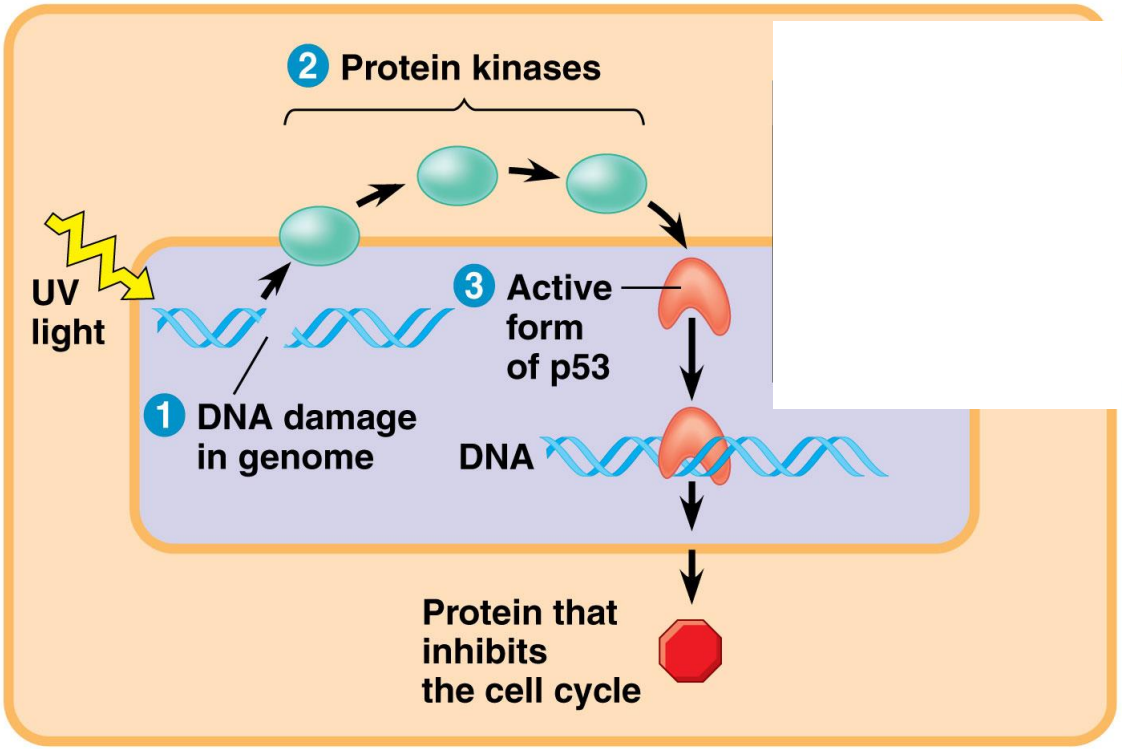


Tumour suppressor genes



p53 gene encodes the p53 **transcription factor** which is a component of signal transduction pathways.

p53: an example of a Tumour suppressor gene



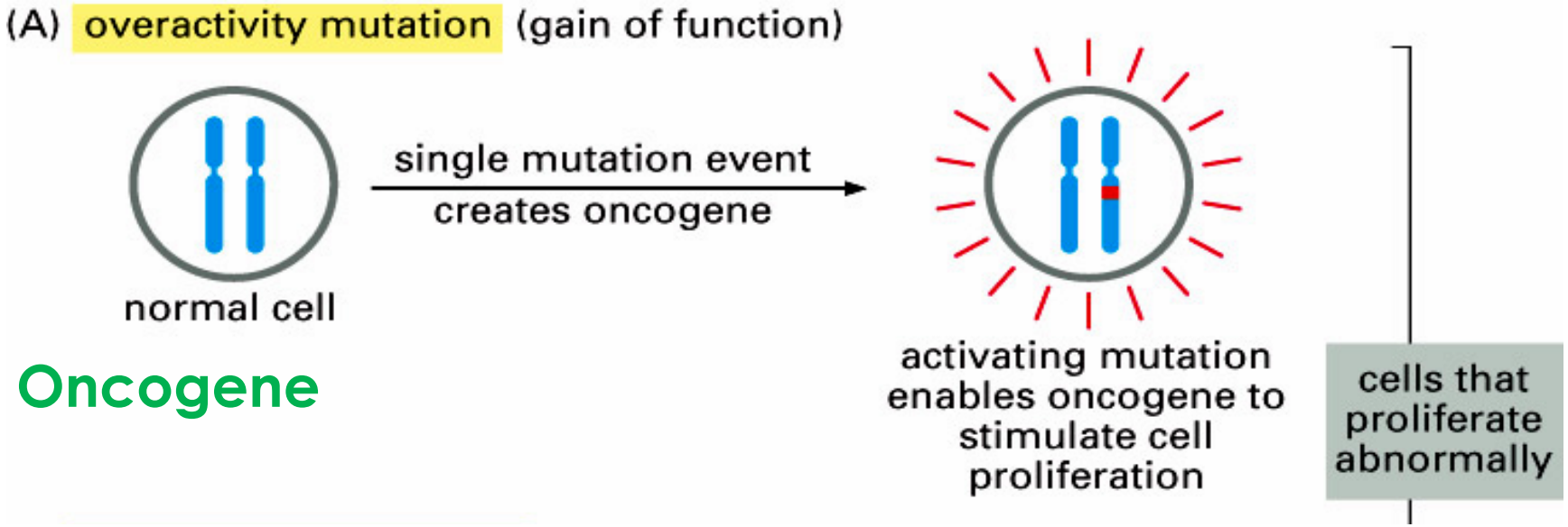
(b) Cell cycle–inhibiting pathway

p53 gene: "Guardian" of the genome

With DNA damage, **p53** will activate several other genes.

- Activate a gene called p21, whose product will halt the cell cycle by binding to cyclin-dependent kinases ➔ time to repair DNA.
- "turn on" genes for DNA repair
- When DNA cannot be repaired, p53 activates apoptotic genes

SUMMARY: Mutation of Proto-oncogenes and Tumour Suppressor Genes



Oncogene

Summary: Role of oncogene and tumor suppressor genes in the development of cancer

[i.e. breakdown on gene regulation]

Mutations in genes are associated to cancer

a) Proteins that stimulate cell division:

- **Proto-oncogenes (normal) → oncogenes (cancer)**: eg. Ras
- Dominant, gain-of-function:

b) Proteins that inhibit cell division:

- **Tumour suppression genes**
- Prevent uncontrolled cell growth. eg. p53
- Recessive, loss-of-function

(A) Genes that regulate the cell cycle are mutated behave differently (Upset of cell cycle controls)

Normal cells: G1→ S transition is tightly regulated

- Cell cycle stimulating pathway (e.g. Ras) → proto-oncogene
- Cell cycle inhibiting pathway (e.g. p53) →tumour suppressor genes

Tumour cells: G1→ S transition is disturbed

- Cell cycle stimulating pathway (e.g. Ras) constantly active
- Cell cycle inhibiting pathway (e.g. p53) is NOT active

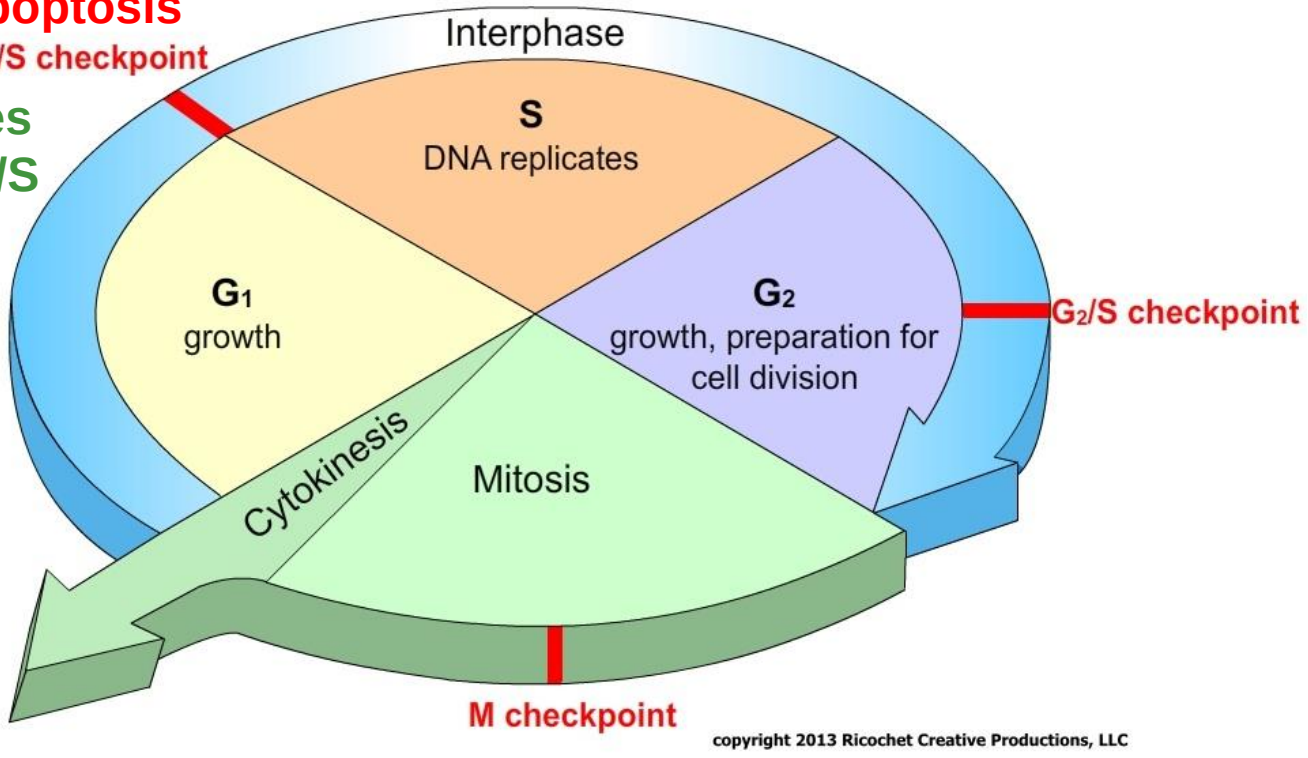
→Hence, in both situations, cells with these mutated genes (e.g. Ras and p53) grow uncontrollably → cancer

Normal cells have specific checkpoints to regulate cell division

Tumour suppressor genes (e.g. p53) ➔ G1 arrest and apoptosis

p53: regulates cyclin A (2nd brake to cell cycle progression

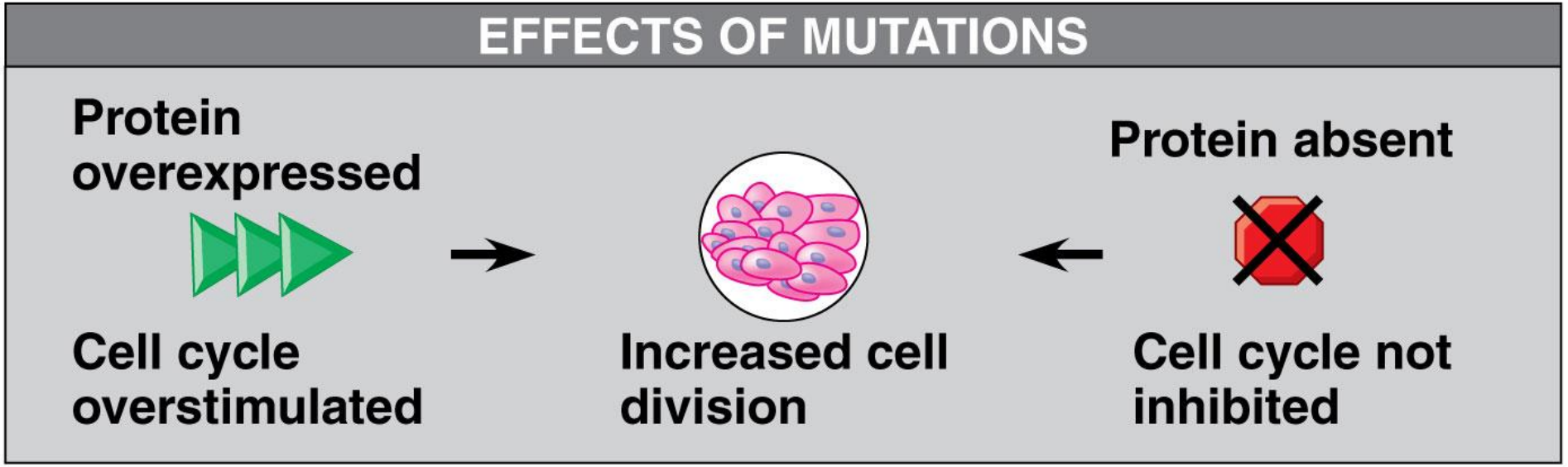
Proto-oncogenes (e.g. Ras) ➔ G1/S checkpoint



Genes that control the progression of cell cycle are mutated and are not able to function properly:

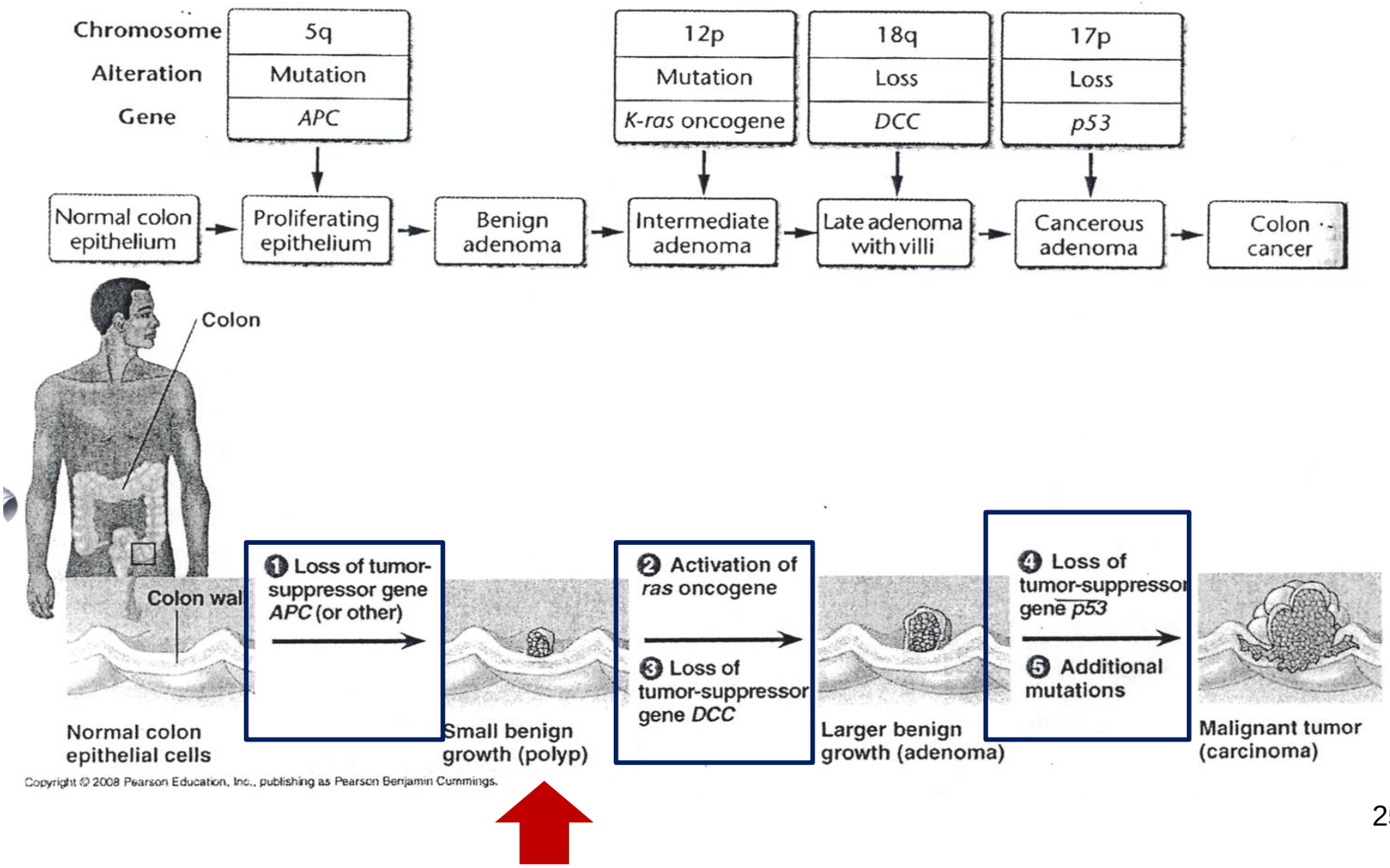
Proto-oncogene

Tumour Suppressor Gene

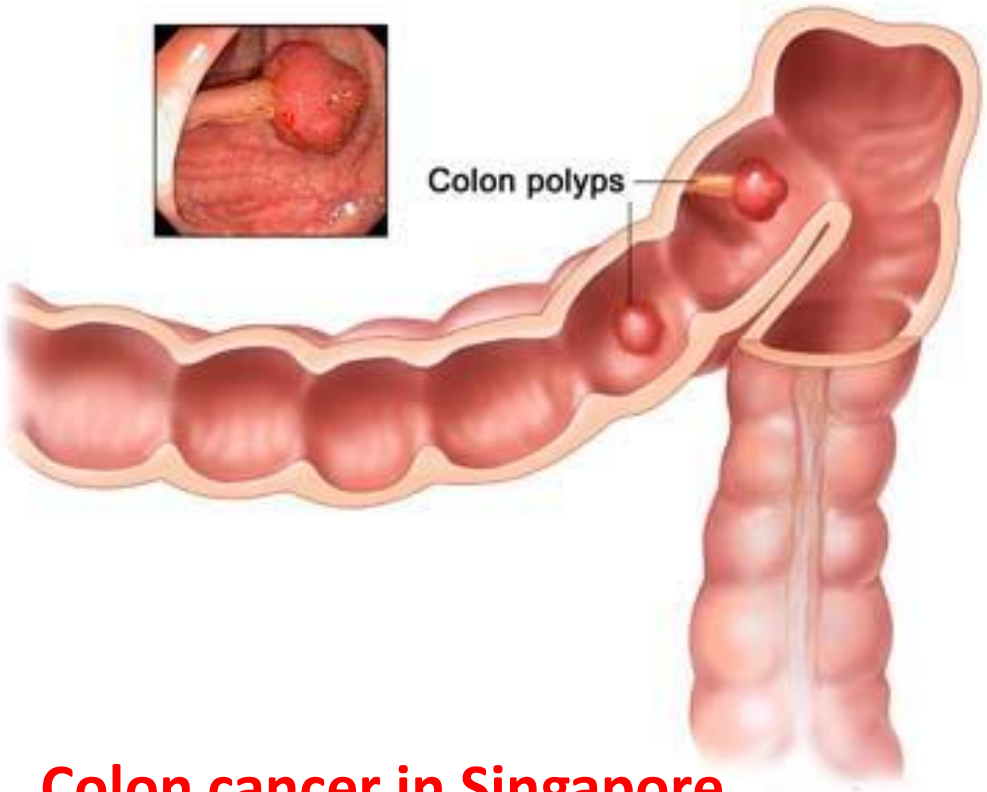


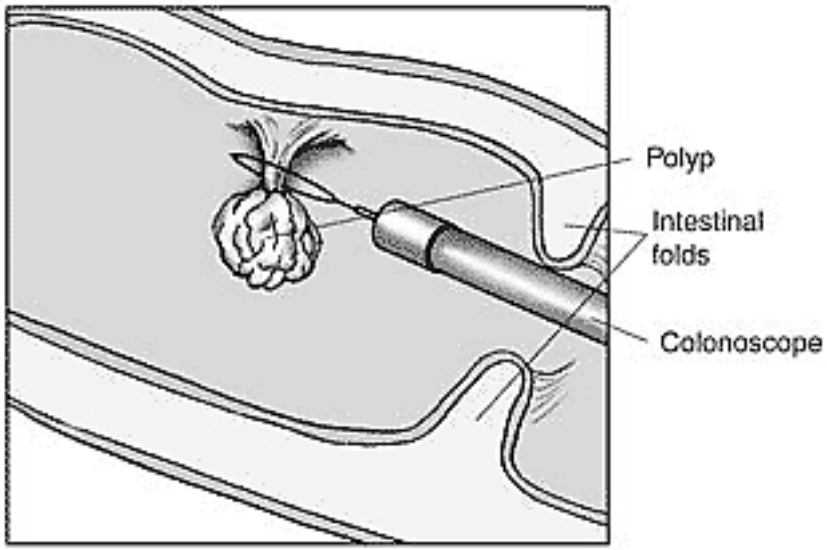
(c) Effects of mutations

Cancer is a multi-step process and accumulates with time (e.g. Colon cancer)



Colon polyps



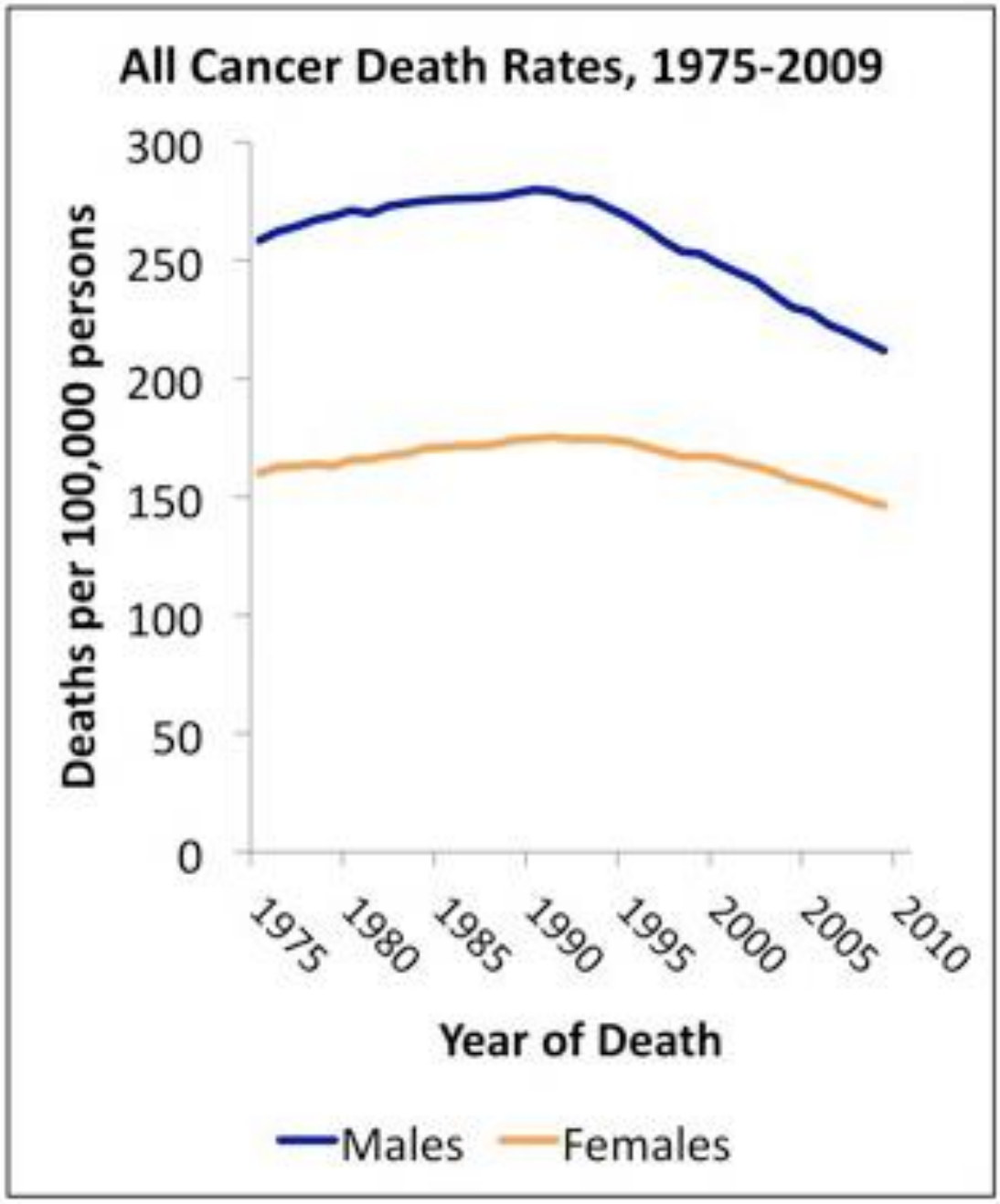


Colon cancer in Singapore

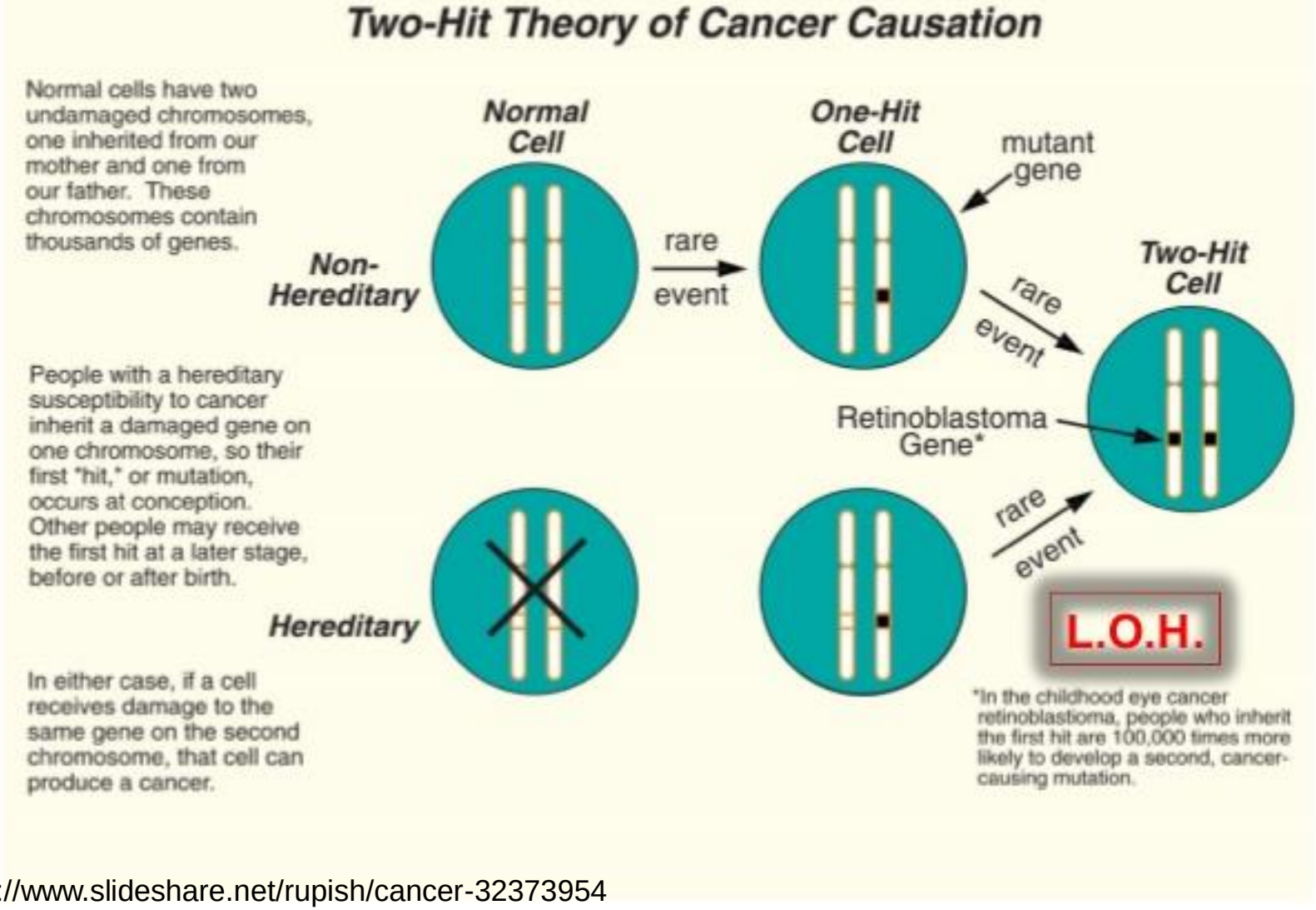
#1 killer for men

#2 killer for women

http://digestive.niddk.nih.gov/ddiseases/pubs/colonpolyps_ez/


All Cancer Death Rates, 1975-2009
Deaths per 100,000 persons
300
250
200
150
100
50
0
1975
1980
1985
1990
1995
2000
2005
2010
Year of Death
Males
Females

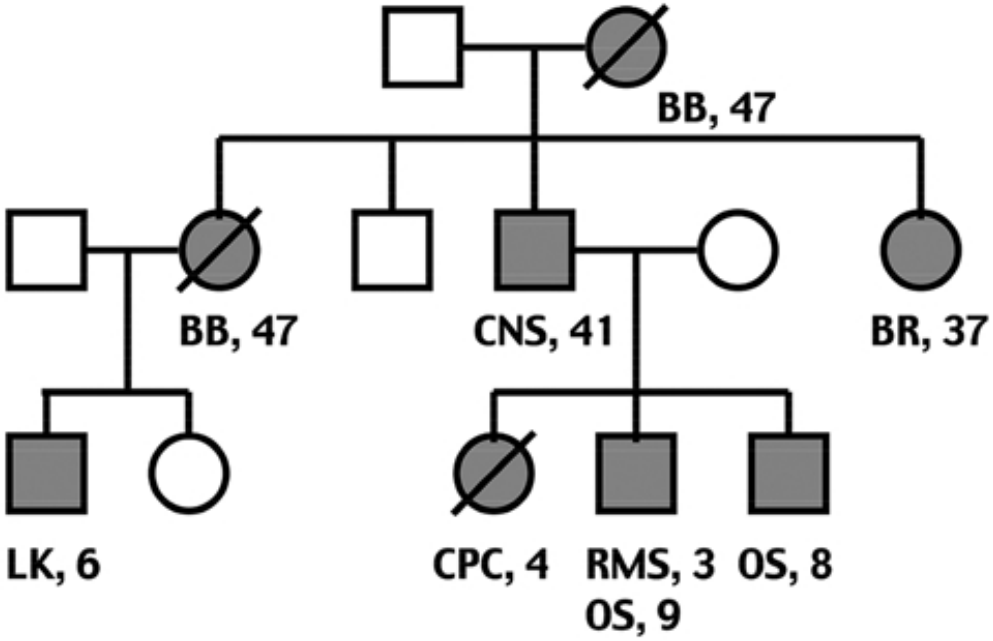
(B) Family history of Cancer (Genetics and Cancer)



https://www.slideshare.net/rupish/cancer-32373954

p53 inheritance (Li Fraumeni syndrome)

Due to a **germ-line mutation** of the p53 tumour suppressor gene



Pedigree of a family with Li-Fraumeni syndrome.

Filled circles/squares represent affected members; slashes represent deceased family members. **Numbers represent age at diagnosis**.

BB = **bilateral breast cancer;**
CNS = **brain tumor**;
BR = **unilateral breast cancer**;
LK = l**eukemia**;
CPC = **choroid plexus carcinoma**;
RMS = **rhabdomyosarcoma**;
OS = **osteosarcoma**.

Case study of Li Fraumeni Syndrome (LFS)

END