Cancer

1. Introduction

Cancer is a range of diseases that is characterised by uncontrolled cell growth and division, as well as the subsequent spread of abnormal cells to surrounding tissues and other parts of the body. Many describe cancer as a genetic disease, and indeed so, for it results from the accumulation of mutations of cancer critical genes that lead to uncontrolled cell growth and proliferation. It can also result from the loss of normal cell cycle and growth control.

Understanding the multi-step development of tumors and cancers enable us to develop specific interventions for cancer treatment. In this part of the lecture series, you will gain an understanding of the various factors that cause cancer, the cancer critical genes and changes to them that result in cancer, as well as appreciate how cancer development is a multistep process.

2. Learning Outcomes

2 (p) Identify the causative factors, including genetic, chemical carcinogens, ionising radiation and loss of immunity, which may increase the chances of cancerous growth.

2 (q) Explain how the loss of function mutation of tumour suppressor genes, including p53, and gain in function mutation of proto-oncogenes, including ras, results in uncontrolled cell division.

2 (r) Describe the development of cancer as a multi-step process that includes accumulation of mutations, angiogenesis and metastasis.

3. References

Campbell, N.A. and Reece, J.B. (2008). Biology, 8th edition. Pearson.

4. Organisation of Lecture Content

Notes to self

5. Overview

5.1 Definition of Cancer

- Cancer is a group of diseases characterized by
  - **Uncontrolled cell division** and
  - **Metastasis: the spread of abnormal cells** to surrounding tissues and other parts of the body.

5.2 Dysregulation of cell cycle checkpoints and its link to cancer

- Recall that you have learnt about the cell cycle checkpoints in the topic of Mitosis and Meiosis. Important points to note are summarized in the following table:

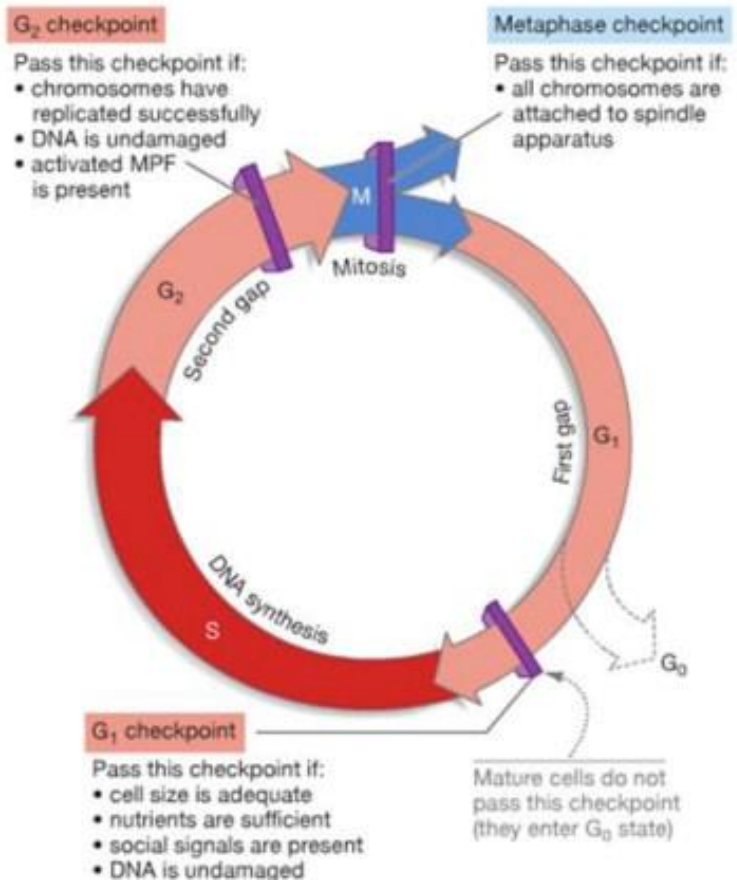


Figure 1. Checkpoint controls in cell cycle. Each of the G1, G2 and M checkpoints triggers the essential processes of the cell cycle: DNA replication, mitosis and cytokinesis respectively

Checkpoint	What is checked?	Consequences of Dysregulation
G1	• Most important checkpoint to decide if cell should divide or not (G_0 phase is the non-dividing phase). • Assesses if the **environmental conditions** (sufficient growth factors and nutrients, absence of DNA damage and adequate cell size) are favourable for cell division.	If G1 checkpoint is defective but the cell still enters the S phase, the **subsequent phases of the cell cycle (including DNA replication and mitosis) might not occur properly**.
G2	• This checkpoint triggers the start of M phase (nuclear division) • Assesses if **DNA replication is completed** and **cell size is adequate**.	If G2 checkpoint is defective but cell still enters the M phase when not all chromosomes have been replicated, the **chromosome number in daughter cells would be affected.**
Metaphase (spindle assembly)	• Last cell cycle checkpoint • Assesses if **all chromosomes are attached to the mitotic spindle**. If the centromeres are not attached properly to the kinetochore microtubules, entry into **anaphase is prevented**.	If Metaphase checkpoint is defective but cell still enters anaphase, **aneuploidy** (extra or missing chromosome) or **polyploidy** (extra sets of chromosomes) would result.

- The dysregulation of cell cycle checkpoints can result in uncontrolled cell division where the **rate of cell division exceeds cell death**, **leading to tumour formation**.

5.3 Types of tumours

Notes to self

- The formation of tumours occurs in the development of cancer. However, having a tumour does **not** mean an individual has cancer.
- There are 2 types of tumours, based on their pattern of growth and invasive capacity:
    - **Benign tumour**: refers to a mass of cells that **keeps on dividing and does not die off readily**. However, the cells **grow locally and cannot spread** to other regions of the body. Benign tumours are non-cancerous.
    - **Malignant tumour**: occurs when the mass of cells gain the ability to 1. **Invade surrounding tissue** (erode normal surrounding tissue) and 2. **Metastasise** (can spread to other parts of the body).
- Most cancers originate from a **single aberrant cell** that proliferates out of control to give rise to a **primary tumour** whose cells eventually metastasise via the **blood stream or lymphatic vessels** to form **secondary tumours**.

6. Molecular Basis of Cancer

6.1 Cancer as a genetic disease

- The vast majority of cancers are initiated by **genetic mutations**.
- Gene mutations may be **inherited**:
    - If the mutations to cancer critical genes occur in **germ line cells** (**reproductive cells of the body e.g. sperm and egg**), they can be passed down to the next generation.
    - Some people thus inherit a higher susceptibility to a single form or multiple forms of certain cancers.
- Gene mutations may be **acquired** in an individual's lifetime:
    - These mutations could result from errors that occur during cell division. They could also be caused by exposure to certain chemical substances (carcinogens) or ultraviolet rays that cause DNA damage (More details in Section 7 on Factors which Increase the Chance of Cancer Occurrence).

Notes to self

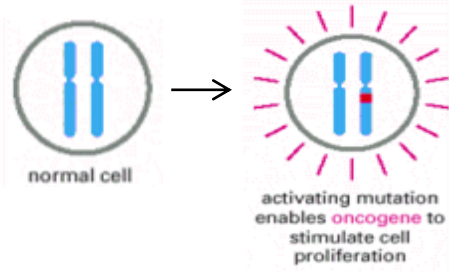
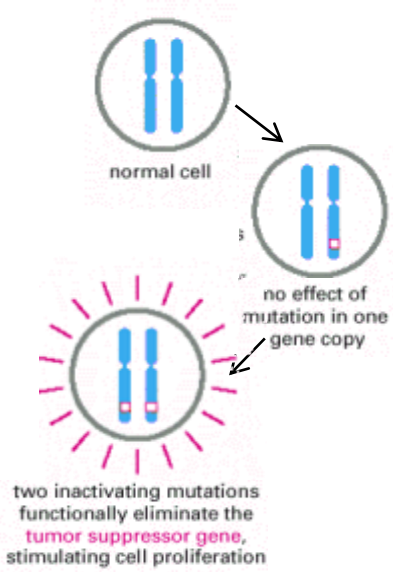
- How can genetic mutations affect normal cells?
    - **They can cause a normal cell to continue to divide.**
      - The mutation of normal **proto-oncogenes** to **oncogenes** instructs normal cells to grow and divide **excessively**. As these mutated cells undergo mitosis, all the genetically identical daughter cells carry the same mutation.
    - **They can fail to stop uncontrolled cell growth**
      - Normal cells have the ability to **stop dividing when they are in sufficient numbers** in the body. However, cancer cells having a **mutation** in their **tumour suppressor genes** lose this ability and thus continue to divide.
    - **They can have mistakes during DNA repair**
      - Normal cells have **functional DNA repair genes that control the correct repair of errors in a cell's DNA**. A **mutation in the DNA repair genes** will lead to errors in DNA remaining uncorrected. When cells **accumulate** these errors (mutations), they become cancerous.

- The development of cancer is a **multi-step process**. **Multiple somatic mutations** are required to produce all the changes characteristic of a full-fledged cancer cell. Thus cancer is the result of an **accumulation of mutations to a cell's DNA over time**.

6.2 Genes involved in cancer development

- The key genes involved in the development of cancer are:
    1. Proto-oncogenes
    2. Tumour Suppressor genes
    3. Gene encoding telomerase
    4. Genes encoding proteins involved in angiogenesis
    5. Genes encoding proteins involved in metastasis

- These genes either undergo a **gain-of-function** or a **loss-of-function** mutation during cancer development.
- The following table summarises and compares gain-in function and loss-in-function mutations:

	Gain-of-function mutation	**Loss-of-function mutation**
Definition	1. A mutation that causes a gene **to encode proteins with <u>new or enhanced activity</u>.** 2. Gene products of **<u>proto-oncogenes</u>** can become/are: 1. hyperactive/ 2. resistant to degradation/ 3. produced in excessive amounts	1. A mutation that causes a **<u>gene product to be non-functional</u>**. 2. Gene products of **<u>tumour-suppressor genes</u>**: 1. are defective and 2. cannot activate other genes.
Type of genes the mutation affects	Affects **proto-oncogene**, e.g. ***ras* gene** A mutated proto-oncogene is known as an **<u>oncogene</u>**	Affects **tumour suppressor gene**, e.g. ***p53* gene**
Number of alleles that has to be mutated in order to be cancerous	Only **<u>one copy of the allele</u>** need to be mutated. This is known as **<u>dominant mutation</u>**. - mutation in just one copy is enough to give **increased number of** gene products / a **hyperactive** gene product/ **degradation resistant** gene product. 1. A normal cell is sensitive to the amount of such gene products. Any extra means cell cycle escapes normal control.  	**<u>Both copies of allele</u>** need to be mutated. This is known as **<u>recessive mutation</u>**. - if one is mutated, there is **still another copy of the normal allele that can function normally** (e.g. its products can still activate other genes for DNA repair). 
Effect on cell cycle (in cancer cells)	Overstimulate cell cycle Cells proliferate excessively	Unable to halt cell cycle to repair DNA damage. Cells with accumulated mutations keep dividing.
Type of mutation	**Dominant** mutation	**Recessive** mutation

Notes to self

6.2A Proto-oncogenes

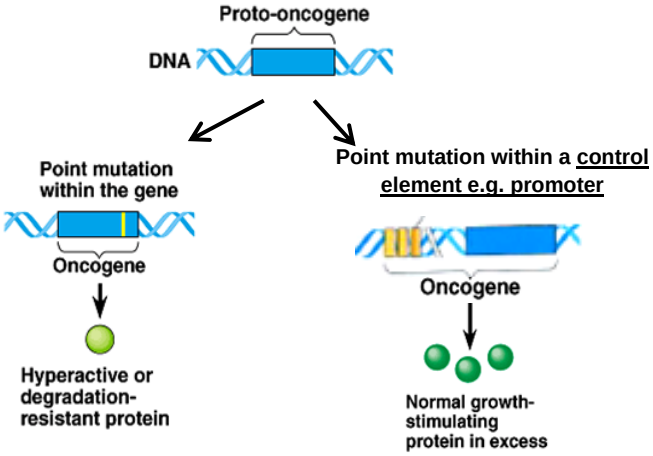
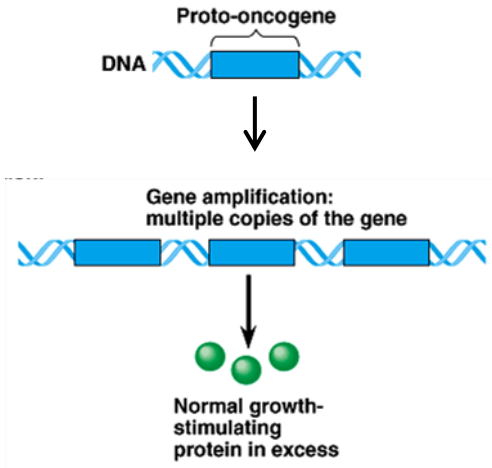
- Proto-oncogenes are **normal cellular genes** that **codes for proteins** that **stimulate normal cell growth and proliferation**.

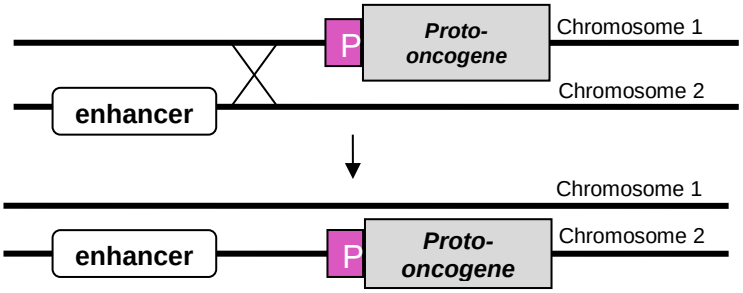
- Proto-oncogene products are:
  - Proteins derived from proto-oncogenes
  - Involved in stimulating **normal** cell growth and division
  - E.g. Growth factors, growth factor receptors, transcription factors etc.

- Mutated proto-oncogenes are known as **oncogenes**.
- This mutation that converts proto-oncogene to oncogene is a **gain-of-function mutation**. The mutation results in an **increase** in the
  - **Amount** of proto-oncogene protein product or
  - The **intrinsic activity** of the protein product.

- Mutation mechanisms that lead to oncogene formation include:
  1. Point mutations in a control element or proto-oncogene itself
  2. Amplification of the proto-oncogene
  3. Movement of DNA within the genome
     i. Chromosomal Translocation
     ii. Gene Transposition
     iii. Retroviral Integration

Table explaining mutations that convert proto-oncogenes to oncogenes

Type of genetic change	Description
Point mutations	▪ A point mutation occurring in the **coding sequence** of the proto-oncogene → Changes the **amino acid sequence** of the proto-oncogene protein → Thus changing the protein to be either i) more active **(hyperactive)** or ii) more resistant to degradation **(degradation-resistant gene product)** than the normal protein. ▪ A point mutation occurring in base sequences of regulator elements (e.g. the promoter that controls a proto-oncogene), → Leads to the **upregulation of proto-oncogene expression** → Thus an **excess production** of the growth stimulating protein. 
Amplification of a proto-oncogene	Gene amplification results in an **abnormal increase in the number of copies** of the proto-oncogene in the cell. → Leads to the **excessive production** of proto-oncogene protein → Thus promoting **excessive cell division.** 

Movement of DNA within the genome	
▪ **Chromosomal translocation**	If a proto-oncogene that **translocated as part of a chromosome segment** ends up **near an especially active (hyperactive) promoter**, for example, its transcription may increase, making it an oncogene.
▪ **Gene transposition**	**Transposition** of a proto-oncogene such that it comes **under the control of a more active promoter** OR **enhancer** (illustrated below) OR **transposition of a more active promoter** adjacent to a proto-oncogene.  All these instances result in the **upregulation of proto-oncogene expression**.
▪ **Retroviral integration**	Integration of viral genome into a proto-oncogene can convert it to an oncogene, causing **insertional mutagenesis**, resulting in the altered protein product that might lead to excessive cell division.

Example of proto-oncogene: *ras* gene

- The normal *ras* gene encodes Ras proteins, which are involved in signal transduction pathways. (Note: details on signal transduction pathways and Cell Signalling will be covered in a future lecture).

- A brief outline of events that involve the **normal *ras* gene** is as follows:
  - Growth factor binds to its receptor embedded on the cell surface membrane.
  - This binding triggers a series of reactions inside a cell, stepwise as follows:
    - GTP binds to inactive Ras protein, thus activating it.
    - Active Ras proteins **transduce (pass down) signals from the growth factor** to downstream signalling processes.
    - Eventually, **cell cycle will be stimulated and the cell undergoes cell division**.

Notes to self

- **Mutation in ras gene** results in a **constitutively active Ras protein**. This means that the Ras protein is **always bound to GTP and is thus permanently activated**. This would lead to **increased cell division** even in the **absence of growth factor** binding to its receptor.

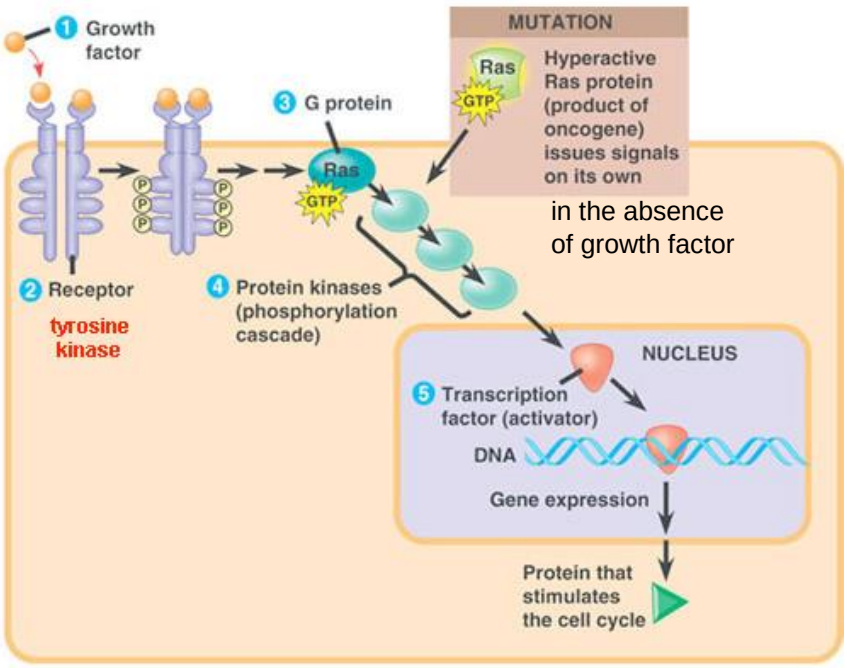


Figure 2. Normal Ras protein signal transduction pathway in response to growth factor binding to their receptors. Figure is also annotated with what happens when the ras protein is encoded by the oncogene instead of the proto-oncogene.

6.2B Tumour Suppressor Genes

- Tumour suppressor genes are **normal cellular genes** that **code for proteins** that normally **inhibit cell growth and division**.

- Tumour suppressor gene products:
  - Are **proteins** derived from tumour suppressor genes
  - Activate **cell cycle arrest**, **DNA repair** and /or **apoptosis** (programmed cell death)

- Mutated tumour suppressor genes contribute to cancer when there is a **loss-of-function mutation**. The mutation causes the expressed protein to **lose its ability to inhibit cell growth and division**.

Example of tumour suppressor gene: *p53* gene

Notes to self

- The *p53* gene is the most commonly mutated gene in human cancers. About 50% of all human cancers are associated with mutations in this gene.

- The *p53* gene **encodes a *p53* protein product** that **functions as a specific transcription factor / activator protein**.

- ***p53* protein binds to DNA (at the enhancer region)** to **promote** synthesis of **cell cycle-inhibiting proteins** (i.e. proteins that act to **repair DNA damage**, **cause cell cycle arrest** or **apoptosis** if DNA damage is beyond repair.

- The ***p53* gene** plays an important role in the following processes when there is DNA damage:

  A. Cell cycle arrest
  - The p53 protein **activates a specific gene** whose product **halts the cell cycle**.
  - This is so that the **cell with damaged DNA** has **more time to repair its DNA** to prevent the production of mutant daughter cells.

  B. DNA repair
  - The *p53* protein can **turn on genes** whose **protein product can directly repair DNA.**
  - This **preserves genomic integrity and prevents mutations** that may lead to the **formation of oncogenes** and **inactivate other tumour suppressor genes**.

  C. Apoptosis (Programmed Cell death)
  - The *p53* protein **activates other genes** whose **protein product cause cell death** so that **damaged cells are removed.** This is important as it removes cell with potential to cause cancer.

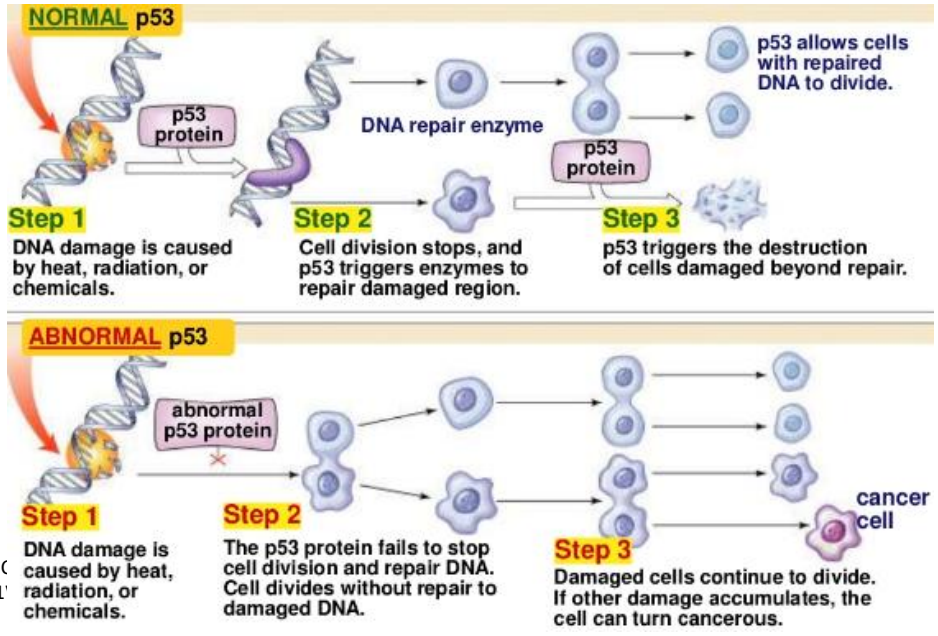


Figure 3 shows the roles of normal p53 protein encoded by normal p53 tumour suppressor gene , contrasted with the abnormal p53 protein encoded by mutant p53 tumour suppressor gene that can cause cancer.

6.2C Genes encoding telomerase

Notes to self

- **Normal somatic cells** have a **natural limit** on the number of times they can **divide**, due to the **shortening of the telomeres** with each round of DNA replication (**end replication problem)**. Hence eventually, once the critical length of telomeres is reached, the normal cells **stop dividing and undergo senescence** (natural cell death due to age).

- Cancer cells however, have the ability to undergo **uncontrolled cell division**.

  What enables these cancer cells to keep dividing repeatedly?
  - Unlike in normal somatic cells where the gene encoding telomerase is switched off, the **gene encoding telomerase in cancer cells is activated**.
  - Hence cancer cells **overcome the end replication problem** and can **lengthen shortened telomeres** with the expression of telomerase.
  - Telomerase activation **confers cancer cells immortality** and enables them to divide repeatedly.

6.2D Genes encoding proteins involved in angiogenesis

- In **later stages** of cancer development, tumours undergo angiogenesis.
- **Angiogenesis** is the process where **new blood vessels form within and around a growing mass of tumour cells**.
- This process is possible because the **expression of genes encoding angiogenic factors** (proteins) is **upregulated**.

- The network of blood vessels enable the tumour mass to **grow beyond the limits imposed by passive diffusion**.
  This is because the tumour cell mass can now:
  - **Obtain nutrients and oxygen more efficiently**
  - **Remove metabolic waste products**

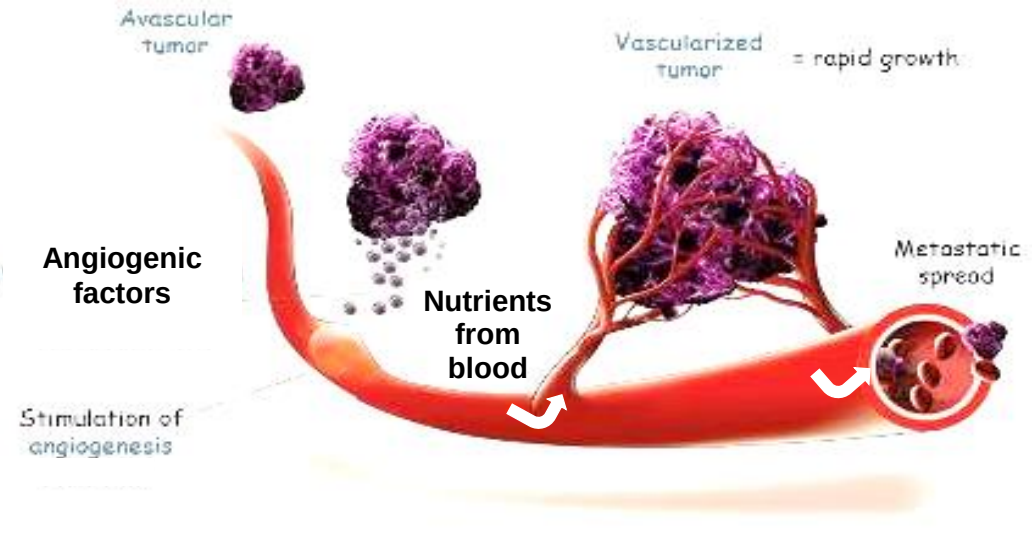


Figure 4 shows the process of angiogenesis: the development of new blood vessels around

6.2E Genes encoding proteins involved in metastasis

- **Metastasis** is the process whereby cells from the localised **primary tumour**:
  - Leave the tumour cell mass and
  - Invade adjacent tissue,
  - Travel to another part of the body by the bloodstream or lymphatic system and
  - Establish themselves as **secondary tumours**.

- In order to metastasise, tumour cells also alter the expression of certain genes:
  - **Down-regulate genes that express proteins responsible for cell-cell adhesion**.
  - **Up-regulate the expression of genes encoding extracellular proteases**.
    - Proteases expressed are required to **breakdown the cytoskeleton and filaments** that hold the cells together.
    - This facilitates **invasion** of cancer cells into the bloodstream and lymphatic system.

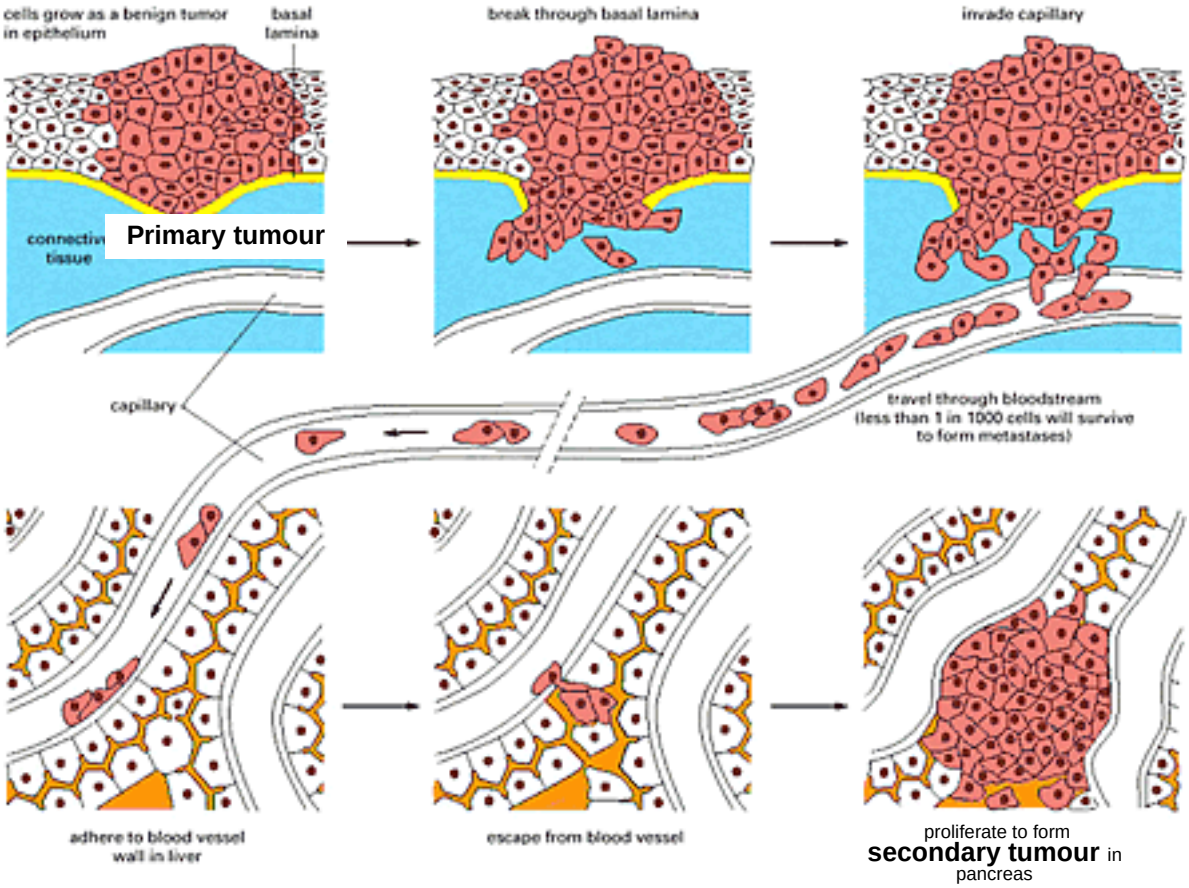


Figure 5 shows metastasis of cancer cells from a primary tumour into the pancreas and the formation of a secondary tumour.

6.3 Summary:

6.3.A The Multi-step Process of Cancer

Notes to self

- The development of cancer requires **a single cell** to **accumulate mutations** in the genes which **control regulatory checkpoints** of the cell cycle.

- With the **disruption of the normal cell cycle**, the cell then undergoes **excessive cell growth and proliferation** resulting in **uncontrolled cell division**.

- Gene mutations that occur include:

    - A **gain-in-function mutation**, which is a **dominant** mutation where mutation in just **one allele of a proto-oncogene** converts it into an **oncogene.**
        - This in turn will result in the production of **excessive amounts of growth factors, or production of hyperactive/degradation resistant growth factors**, leading to excessive cell proliferation

    - A **loss-in- function mutation,** which is a **recessive** mutation where mutations in **both alleles of a tumour suppressor gene**
        - This will **cause a loss of their ability to inhibit cell cycle, enable DNA repair and induce apoptosis**.
    - There will also be **upregulation** of the gene coding for **telomerase to overcome the end replication problem,** so that telomeres can be lengthened and the cell can thus **divide indefinitely**.

- Multiple mutations that remain unrepaired in a single immortal cell which continues to divide will continually accumulate more mutations. **Loss of contact inhibition** will enable the cells to **proliferate into a tumour.**

- **Genes encoding proteins responsible for angiogenesis** are also up-regulated. Angiogenic factors secreted by tumour cells help p**romote the growth of blood vessels around and within the tumou**r. Sustained angiogenesis enables **nutrients and oxygen to be supplied** to the tumour and to **optimise their proliferation**.

- **Genes encoding proteases** are up-regulated as well. They help give cancer cells their **invasive property** and **promote metastasis**, enabling them to infiltrate into the bloodstream and lymphatic system and migrate from a **localised primary tumour** to another part of the body, eventually establishing themselves as **secondary tumours**.

- The above steps should occur for cancer to develop.

- As it takes years to **accumulate** these mutations, developing cancer **increases with age.**

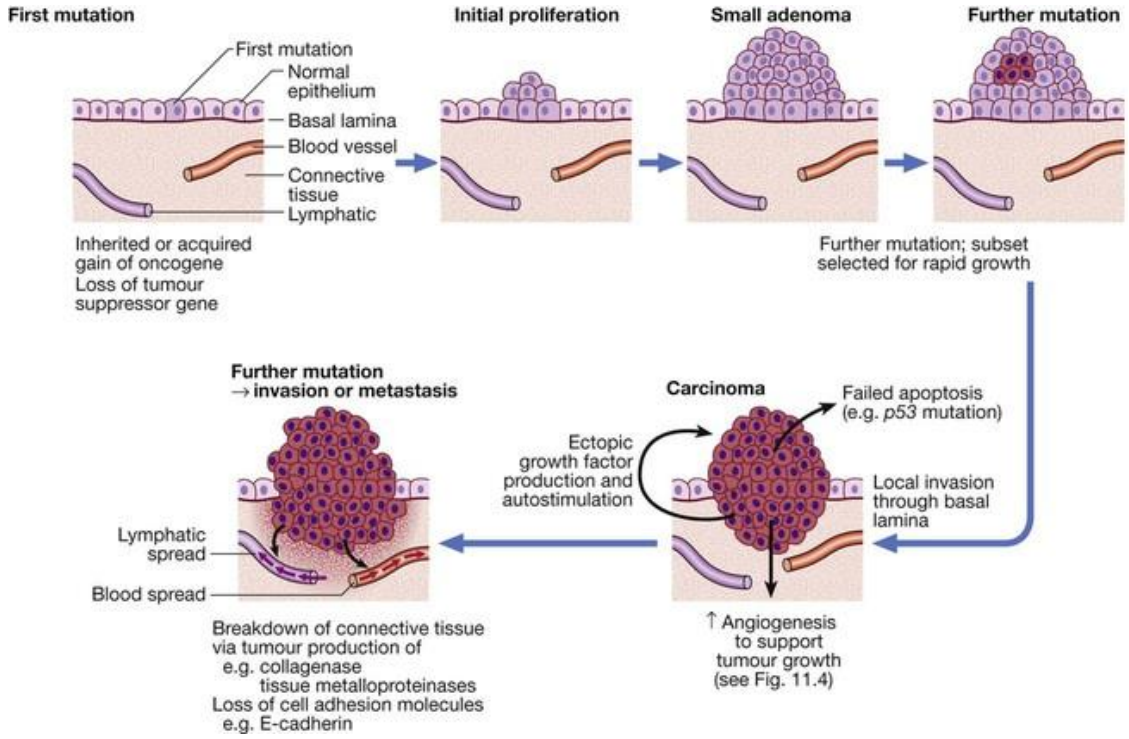


Figure 6 **The Multi-step process of cancer.**

6.3.B Differences between normal and cancer cells

Feature	Normal cells	Cancerous cells
1. Proto-oncogene	Normal cells have **proto-oncogenes**, whose functions are to promote the normal growth and division of cells. Rate of cell division is regulated.	Cancerous cells have **oncogenes**, which are the mutated form of proto-oncogenes. Gain of function mutation result in excessive cell division.
2. Cell division	Show **controlled cell division**.	Oncogenes cause **uncontrolled cell division.**
3. Nuclei / mutation	**Normal nuclei** present.	Cancer cells have **abnormal nuclei**. The **chromosomes have mutated**; some parts of the chromosome may be **duplicated** and some **deleted**.
4. Apoptosis	Normal cells show **programmed cell death/apoptosis**. They divide for a certain number of times and then stop dividing. This is regulated by tumour suppressor genes (e.g. ***p53* gene**)	Cancerous cells **do not show apoptosis**. They can divide indefinitely.

5. Contact inhibition	Normal cells show **contact inhibition**. This means that they do not divide further when in contact with other cells.	Cancerous cells **do not show contact inhibition**.
6. Differentiation	Normal **cells differentiate** to become **specialized cells**. Specialized cells, such as nerve cells, do not divide.	Cancerous **cells fail to differentiate** properly.
7. Tumour suppressor gene	Presence of **tumour suppressor genes**.	**Tumour suppressor genes are absent** or have been **mutated** (resulting in loss-in- function of tumour suppressor genes). Cells are thus unable to carry out the following processes properly: - repair DNA damage - arrest aberrant cell cycle - Promote apoptosis
8. Cell adhesion / metastasis	Cell adhesion →Formation of tissue and organs	Can detach from surrounding cells, establish themselves as secondary tumours
9. Angiogenesis – formation of blood vessel	Does not stimulate new blood vessels	Stimulates growth of new blood vessels within tumours.

7. Factors which increase the chance of cancer occurrence

7.1 Genetic Predisposition/ Heredity

Mutations to cancer critical genes (proto-oncogenes to form oncogenes/ mutated tumour suppressor genes) that occur in **germ line cells** (sperm and egg) can be passed from parent to offspring.

An individual inheriting an oncogene or mutant allele of a tumour suppressor gene will be one step close to **accumulating the necessary mutations** for cancer to develop.

Example: Mutation of *BRCA1 or BRCA2* gene in humans.

- BRCA1 and BRCA2 (**BR**east **CA**ncer) are tumour suppressor genes found in both men and women.

Notes to self

- They encode a normal protein that functions in DNA repair. Mutations in these genes encode defective proteins that are unable to fix DNA damage, thus leading to mutations in other genes and thereby increase the risk of cancer.

- Women who inherit one mutant BRCA1 allele have a 60% risk of having breast cancer before age 50%, as opposed to 2% in women with 2 normal BRCA1 alleles. They also have an increased 55% risk of developing ovarian cancer.

- Men with mutations in the BRCA1 gene also have increased risk of developing breast or prostate cancers.

7.2 Carcinogens

- Carcinogens are agents or substances that are **directly involved in causing cancer**.

- The majority of identified carcinogens are **mutagens**, which are **agents that cause DNA damage and generate mutations**.

- These mutagens include:
  A. Chemical carcinogens
  B. Radiation
  C. Viruses

7.2A Chemical Carcinogens

Example: Tobacco smoke

- Carcinogens in smoke belong to multiple classes, including **nitrosamines, aromatic amines and volatile organic hydrocarbons.**

- Most carcinogens in cigarette smoke are metabolically activated into forms that bind covalently to DNA, forming **DNA adducts**.

  Normally, cellular repair systems remove DNA adducts and maintain DNA structure. However, if DNA repair enzymes are damaged or cannot function efficiently, these DNA adducts remain and increase the chance of developing mutations in somatic cells.

- **Nicotine** in smoke can bind to nicotinic receptors and other cellular receptors. This binding can lead to the activation of protein kinase B and protein kinase A that could **activate signalling pathways** in cells and **result in uncontrolled cell division.**

Notes to self

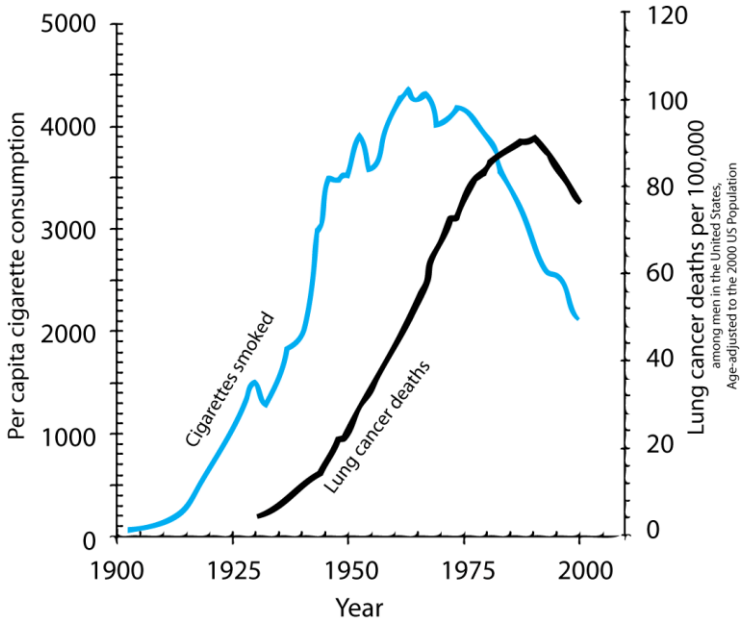


Figure 2. Correlation between smoking and lung cancer deaths

Example: Asbestos

- Asbestos can be found in some construction materials. Asbestos fibers can be released into the air when the asbestos-containing materials are degraded.

- Exposure to asbestos increase people's risk of developing **mesothelioma, a malignant cancer of the membranes in the lungs and abdomen**.

7.2B Radiation

- Overexposure to **ionising radiation** (which includes X-rays and gamma-rays) causes DNA mutations that may lead to cancer.

- Overexposure to **Ultra-violet (UV) radiation** (found in sunlight) can lead to skin cancer.
  - **UV-A** and **UV-B** are two wavelengths of radiation that can penetrate to different depths of the skin.
  - **UV-A** radiation causes **oxidative damage** to skin cell components.
  - **UV-B** radiation can break the hydrogen bond between nitrogenous bonds to break. This causes the unbounded base to interact with adjacent bases on the same DNA strand to form dimers.

Notes to self

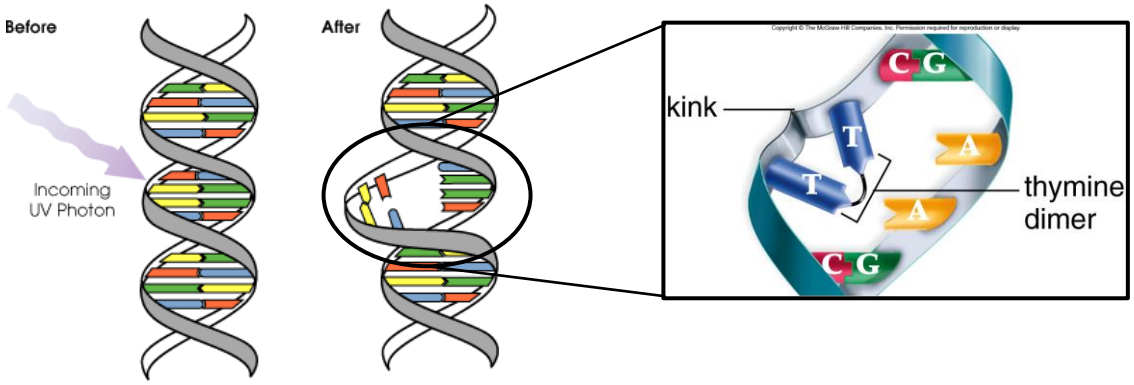


Figure 3. UV radiation causes DNA damage. H bond between nitrogenous base breaks, causing interactions between 2 pyrimidines (thymines) in the case above, forming dimers. These mutations resulting from the formation of pyrimidine dimers frequently arise in the p53 tumour suppressor gene in skin cancers.

7.2C Viruses

- Viruses play a role in about 15% of human cancer cases worldwide. For instance, liver cancer is common in parts of the world (Africa and Southeast Asia) where hepatitis-B viral infections are common. Also, infections with some forms of papilloma virus increase the risk of cervical cancer in women.

- Viruses **integrate their genetic material into the DNA** of infected host cells and contribute to cancer development by:

  Activating a proto-oncogene to an oncogene by **gain of function mutation** or **inactivating** tumour suppressor genes by **loss of function mutaton.**

  Producing proteins that **inactivate p53 and other tumour-suppressor proteins**, thus making the cell more prone to becoming cancerous.

  Introducing an oncogene into a normal cell e.g. retroviruses may carry a copy of host-derived oncogene, which is reverse-transcribed and inserted into the genome of the next infected host cell.

Example: Epstein Barr Virus causes Lymphoma

- **Lymphoma** is a **group of blood cell tumors** that **develop from lymphatic cells**. Hodgkin's lymphoma is a type cancer which originates from a specific type of white blood cells called **lymphocytes**.
- The Epstein-Barr virus (EBV) is the first human virus identified with a proven association with the development of cancer. EBV preferentially infects **B lymphocytes**.

Notes to self

- Antigens encoded by EBV interfere with a number of important cellular pathways, thereby leading to tumor formation. These EBV antigens have been found to **immortalise B cells by facilitating p53 degradation**, enhancing transcription of certain host and viral genes, **blocking apoptosis** and affecting chromatin remodeling processes.

7.2D Loss of immunity

- Patients with **weakened immune systems** have specialised immune cells that are **unable** to carry out their function effectively. This increases their chances of cancerous growth.

- These specialised immune cells include cytotoxic T cells, natural killer cells and macrophages (which will be covered in the extension topic on the Immune System), which detect and induce the death of developing tumour cells.

- E.g. Patients infected with the Human Immunodeficiency Virus (HIV) have weaked immune systems, thus reducing the body's ability to fight infections that may lead to cancer.

7.2E Other Factors

- **Reactive oxygen species (ROS)** can also cause **DNA damage**, possibly leading to cancer development. For example, the high levels of ROS produced during infection by Helicobacter pylori are a causal factor of gastric cancer.
- High levels of bile acids in the colon, which is a result of a **high-fat diet**, also causes DNA damage. This in turn contributes to causing colon cancer.

Keywords include:

Carcinogen	constitutive	Tumour
Uncontrolled cell division	*p53* gene	Angiogenesis
Proto-oncogene	Dominant	P53 protein
Tumour suppressor gene	Recessive	Contact inhibition
Gain in function mutation	Benign	Apoptosis, programmed cell death
Loss of function mutation	Malignant	Cell-cell adhesion
Ras gene	Metastasis	
Ras protein		

Links to Other Topics:

Topic No.	Topic	Comments
1	Cellular Functions (Cell Division)	Cancer cells do not heed the normal signals that regulate the cell cycle. They escape cell cycle checkpoints, undergoing uncontrolled proliferation and cell divisions despite presence of damaged DNA.
3	Genetics of Viruses	Viruses are involved in 10-20% of all cancers. The infection of a cell by such viruses (e.g. retroviruses) leads to the expression of viral proteins that enhance the growth potential/survival of that cell; these viruses either carry a copy of an oncogene or the integration of viral genome leads to altered expression of proto-oncogenes or tumour suppressor genes. Often, the viral infection alone is not sufficient to cause cancer. Over time, coupled with the accumulation of mutations that enhance growth of the cell, cancer may develop.
4	Organisation and Control of Prokaryotic and Eukaryotic Genome (I and II)	In many malignant tumours, the gene for telomerase is activated. Telomerase reverses the shortening of chromosome ends during DNA replication. Production of telomerase in cancer cells removes the natural limit on the number of times the cell can divide.
5	Cellular Physiology and Biochemistry (Cell Signalling & Communication)	Cell signaling pathways can lead to inactivation/activation of protein factors that regulate gene expression.
6	Cellular Physiology and Biochemistry (Cell Signalling & Communication)	The proteins encoded by many proto-oncogenes and tumour suppressor genes are components of cell-signaling pathways, e.g. ras protein and p53 respectively. These proteins convey external signals to the DNA in the cell's nucleus, leading to cell division or inhibition of cell division respectively. The ras protein is a G-protein that relays a signal from a growth factor receptor (receptor tyrosine kinase) on plasma membrane to a cascade of protein kinases. The cellular response at the end of the pathway is the synthesis of a protein that stimulates the cell cycle.