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**QUESTION 1**

**What do you understand by primary or simple obesity?**

Obesity, also called corpulence or fatness, excessive accumulation of body fat, usually caused bythe [consumption](https://www.merriam-webster.com/dictionary/consumption) of more [calories](https://www.britannica.com/science/kilocalorie) than the body can use. The excess calories are then stored as fat, or [adipose tissue](https://www.britannica.com/science/adipose-tissue). Overweight, if moderate, is not necessarily obesity, particularly in muscular or large-boned individuals.



Obesity was traditionally defined as an increase in body weight that was greater than 20 percent of an individual’s ideal body weight—the weight associated with the lowest risk of death, as determined by certain factors, such as age, height, and gender. Based on these factors, [overweight](https://www.britannica.com/science/overweight) could then be defined as a 15–20 percent increase over ideal body weight. However, today the definitions of overweight and obesity are based primarily on measures of height and weight—not [morbidity](https://www.merriam-webster.com/dictionary/morbidity). These measures are used to calculate a number known as [body mass index](https://www.britannica.com/science/body-mass-index) (BMI). This number, which is central to determining whether an individual is clinically defined as obese, parallels fatness but is not a direct measure of body fat. Interpretation of BMI numbers is based on weight status groupings, such as underweight, healthy weight, overweight, and obese, that are adjusted for age and sex. For all adults over age 20, BMI numbers correlate to the same weight status designations; for example, a BMI between 25.0 and 29.9 equates with overweight and 30.0 and above with obesity. Morbid obesity (also known as extreme, or severe, obesity) is defined as a BMI of 40.0 or higher.

**QUESTION 2**

**How does congenital syndrome and drug therapy affect obesity.**

How do genes affect obesity?
Science shows that genetics plays a role in obesity. Genes can directly cause obesity in specific disorders such as Bardet-Biedl syndrome and Prader-Willi syndrome.

However genes do not always predict future health. Genes and behavior may both be needed for a person to be overweight. In some cases multiple genes may increase one’s susceptibility for obesity and require outside factors; such as abundant food supply or little physical activity.

**Pickwickian syndrome**, also called **obesity hypoventilation syndrome**, a complex of respiratory and circulatory symptoms associated with **extreme**[**obesity**](https://www.britannica.com/science/obesity). The name originates from the fat boy depicted in [Charles Dickens](https://www.britannica.com/biography/Charles-Dickens-British-novelist)’s *The Pickwick Papers,* who showed some of the same traits. (By some definitions, to be obese is to exceed one’s ideal weight by 20 percent or more; an extremely obese person would exceed the optimum weight by a much larger percentage.) This condition often occurs in association with [sleep apnea](https://www.britannica.com/science/sleep-apnea), which is another common complication of obesity.

**Fröhlich’s syndrome**, also called **Adiposogenital Dystrophy**, rare childhood metabolic disorder characterized by [obesity](https://www.britannica.com/science/obesity), growth retardation, and retarded development of the genital organs. It is usually associated with tumours of the [hypothalamus](https://www.britannica.com/science/hypothalamus), causing increased [appetite](https://www.britannica.com/science/appetite) and depressed [secretion](https://www.britannica.com/science/secretion) of gonadotropin. The [disease](https://www.britannica.com/science/disease) is named for Alfred Fröhlich, the Austrian neurologist who first described its typical pattern.

**Prader-Willi syndrome (PWS),** a rare [human genetic disorder](https://www.britannica.com/science/human-genetic-disease) characterized by weak muscle tone at birth, small stature, [intellectual](https://www.merriam-webster.com/dictionary/intellectual) disabilities, overeating leading to childhood [obesity](https://www.britannica.com/science/obesity), and high rates of [morbidity](https://www.merriam-webster.com/dictionary/morbidity) and mortality. PWS arises from the deletion or disruption of [genes](https://www.britannica.com/science/gene) in a particular region of [chromosome](https://www.britannica.com/science/chromosome) 15. First described in 1956 by Andrea Prader, Heinrich Willi, and others, it occurs in approximately 1 of 15,000 live births.

**How do drugs cause weight gain and obesity**

As you can imagine, it can be difficult to pin down exactly why a person is gaining weight. Drugs can affect weight in many ways, and it isn’t always by increasing fat storage. Here are five main reasons for medication-related weight gain:

1. **Increased appetite:** Some drugs, like certain steroids and antidepressants, can stimulate your appetite, so you eat more. If you’re not changing anything else about your diet or exercise activity, this can lead to extra pounds.
2. **Fluid retention**: Some drugs like the diabetes drug, pioglitazone, make the body hold onto more salt, which in turn leads to water build up. So it’s not fat that’s causing weight gain; it’s water.
3. **Increased fat storage**: Some drugs increase weight by affecting how much fat you can store. One example is insulin. Insulin is a growth hormone, which means it stimulates the body to create tissues, including fat cells.
4. **Slowed metabolism**: Some drugs (like beta-blockers for high blood pressure) can cause the body’s metabolism to slow down, which means that calories are not burned as quickly.
5. **Difficulty exercising:** Then there are drugs that make it more difficult to get up and exercise, so you burn fewer calories each day. Some antihistamines can make you sleepy, so you don’t feel like exercising. Others drugs — like amitriptyline and similar antidepressants — can make it more difficult to breath, so it’s harder to exercise.

**QUESTION 3**

**Outline the etiology of cancer and its molecular basis**

Cancers are a large family of diseases that involve abnormal [cell growth](https://en.wikipedia.org/wiki/Cell_growth) with the potential to invade or spread to other parts of the body. They form a subset of [neoplasms](https://en.wikipedia.org/wiki/Neoplasm). A neoplasm or tumor is a group of cells that have undergone unregulated growth and will often form a mass or lump, but may be distributed diffusely.

All tumor cells show the [six hallmarks of cancer](https://en.wikipedia.org/wiki/The_Hallmarks_of_Cancer). These characteristics are required to produce a malignant tumor. They include:

* [Cell growth and division](https://en.wikipedia.org/wiki/Cell_growth) absent the proper signals
* Continuous growth and division even given contrary signals
* Avoidance of [programmed cell death](https://en.wikipedia.org/wiki/Apoptosis)
* [Limitless number of cell divisions](https://en.wikipedia.org/wiki/Biological_immortality)
* Promoting [blood vessel construction](https://en.wikipedia.org/wiki/Angiogenesis)
* [Invasion](https://en.wikipedia.org/wiki/Invasion_%28cancer%29) of tissue and formation of [metastases](https://en.wikipedia.org/wiki/Metastasis)

The progression from normal cells to cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression.

Causes

The majority of cancers, some 90–95% of cases, are due to genetic mutations from environmental and lifestyle factors. The remaining 5–10% are due to [inherited genetics](https://en.wikipedia.org/wiki/Heredity). [*Environmental*](https://en.wikipedia.org/wiki/Environment_%28biophysical%29) refers to any cause that is not [inherited genetically](https://en.wikipedia.org/wiki/Heredity), such as lifestyle, economic, and behavioral factors and not merely pollution. Common environmental factors that contribute to cancer death include tobacco (25–30%), diet and [obesity](https://en.wikipedia.org/wiki/Obesity) (30–35%), infections (15–20%), [radiation](https://en.wikipedia.org/wiki/Radiation) (both ionizing and non-ionizing, up to 10%), lack of [physical activity](https://en.wikipedia.org/wiki/Physical_exercise), and pollution. Psychological stress does not appear to be a risk factor for the onset of cancer, though it may worsen outcomes in those who already have cancer.

It is not generally possible to prove what caused a particular cancer because the various causes do not have specific fingerprints. For example, if a person who uses tobacco heavily develops lung cancer, then it was probably caused by the tobacco use, but since everyone has a small chance of developing lung cancer as a result of air pollution or radiation, the cancer may have developed for one of those reasons. Excepting the rare transmissions that occur with pregnancies and occasional [organ donors](https://en.wikipedia.org/wiki/Organ_donation), cancer is generally not a [transmissible disease](https://en.wikipedia.org/wiki/Transmission_%28medicine%29).

**Chemicals**

The incidence of lung cancer is highly correlated with smoking.

Exposure to particular substances have been linked to specific types of cancer. These substances are called [*carcinogens*](https://en.wikipedia.org/wiki/Carcinogen).

[Tobacco smoke](https://en.wikipedia.org/wiki/Tobacco_smoking), for example, causes 90% of lung cancer. It also causes cancer in the [larynx](https://en.wikipedia.org/wiki/Larynx), head, neck, stomach, bladder, kidney, [esophagus](https://en.wikipedia.org/wiki/Esophagus) and [pancreas](https://en.wikipedia.org/wiki/Pancreas). Tobacco smoke contains over fifty known carcinogens, including [nitrosamines](https://en.wikipedia.org/wiki/Nitrosamine) and [polycyclic aromatic hydrocarbons](https://en.wikipedia.org/wiki/Polycyclic_aromatic_hydrocarbon).

Tobacco is responsible for about one in five cancer deaths worldwide and about one in three in the developed world. Lung cancer death rates in the United States have mirrored [smoking](https://en.wikipedia.org/wiki/Tobacco_smoking) patterns, with increases in smoking followed by dramatic increases in lung cancer death rates and, more recently, decreases in smoking rates since the 1950s followed by decreases in lung cancer death rates in men since 1990.

In Western Europe, 10% of cancers in males and 3% of cancers in females are attributed to alcohol exposure, especially liver and digestive tract cancers. Cancer from work-related substance exposures may cause between 2 and 20% of cases, causing at least 200,000 deaths. Cancers such as lung cancer and [mesothelioma](https://en.wikipedia.org/wiki/Mesothelioma) can come from inhaling tobacco smoke or [asbestos](https://en.wikipedia.org/wiki/Asbestos) fibers, or [leukemia](https://en.wikipedia.org/wiki/Leukemia) from exposure to [benzene](https://en.wikipedia.org/wiki/Benzene).

**Diet and exercise**

Diet, [physical inactivity](https://en.wikipedia.org/wiki/Sedentary_lifestyle) and [obesity](https://en.wikipedia.org/wiki/Obesity) are related to up to 30–35% of cancer deaths. In the United States, excess body weight is associated with the development of many types of cancer and is a factor in 14–20% of cancer deaths. A UK study including data on over 5 million people showed higher [body mass index](https://en.wikipedia.org/wiki/Body_mass_index) to be related to at least 10 types of cancer and responsible for around 12,000 cases each year in that country. Physical inactivity is believed to contribute to cancer risk, not only through its effect on body weight but also through negative effects on the [immune system](https://en.wikipedia.org/wiki/Immune_system) and [endocrine system](https://en.wikipedia.org/wiki/Endocrine_system). More than half of the effect from diet is due to [overnutrition](https://en.wikipedia.org/wiki/Overnutrition) (eating too much), rather than from eating too few vegetables or other healthful foods.

Some specific foods are linked to specific cancers. A high-salt diet is linked to [gastric cancer](https://en.wikipedia.org/wiki/Gastric_cancer). [Aflatoxin B1](https://en.wikipedia.org/wiki/Aflatoxin_B1), a frequent food contaminant, causes liver cancer. [Betel nut](https://en.wikipedia.org/wiki/Betel_nut) chewing can cause oral cancer. National differences in dietary practices may partly explain differences in cancer incidence. For example, [gastric cancer](https://en.wikipedia.org/wiki/Gastric_cancer) is more common in Japan due to its high-salt diet while [colon cancer](https://en.wikipedia.org/wiki/Colorectal_cancer) is more common in the United States. Immigrant cancer profiles mirror those of their new country, often within one generation.

**Infection**

Worldwide approximately 18% of cancer deaths are related to [infectious diseases](https://en.wikipedia.org/wiki/Infectious_disease). This proportion ranges from a high of 25% in Africa to less than 10% in the developed world. Viruses are the usual infectious agents that cause cancer but [cancer bacteria](https://en.wikipedia.org/wiki/Cancer_bacteria) and [parasites](https://en.wikipedia.org/wiki/Parasites) may also play a role.

[Oncoviruses](https://en.wikipedia.org/wiki/Oncovirus) (viruses that can cause cancer) include [human papillomavirus](https://en.wikipedia.org/wiki/Human_papillomavirus) ([cervical cancer](https://en.wikipedia.org/wiki/Cervical_cancer)), [Epstein–Barr virus](https://en.wikipedia.org/wiki/Epstein%E2%80%93Barr_virus) ([B-cell lymphoproliferative disease](https://en.wikipedia.org/wiki/B-cell_lymphoproliferative_disease) and [nasopharyngeal carcinoma](https://en.wikipedia.org/wiki/Nasopharyngeal_carcinoma)), [Kaposi's sarcoma herpesvirus](https://en.wikipedia.org/wiki/Kaposi%27s_sarcoma_herpesvirus) ([Kaposi's sarcoma](https://en.wikipedia.org/wiki/Kaposi%27s_sarcoma) and primary effusion lymphomas), [hepatitis B](https://en.wikipedia.org/wiki/Hepatitis_B) and [hepatitis C](https://en.wikipedia.org/wiki/Hepatitis_C) viruses ([hepatocellular carcinoma](https://en.wikipedia.org/wiki/Hepatocellular_carcinoma)) and [human T-cell leukemia virus-1](https://en.wikipedia.org/wiki/Human_T-cell_leukemia_virus-1) (T-cell leukemias). Bacterial infection may also increase the risk of cancer, as seen in [*Helicobacter pylori*](https://en.wikipedia.org/wiki/Helicobacter_pylori)-induced [gastric carcinoma](https://en.wikipedia.org/wiki/Gastric_carcinoma). Parasitic infections associated with cancer include [*Schistosoma haematobium*](https://en.wikipedia.org/wiki/Schistosoma_haematobium) ([squamous cell carcinoma of the bladder](https://en.wikipedia.org/wiki/Bladder_cancer)) and the [liver flukes](https://en.wikipedia.org/wiki/Liver_fluke), [*Opisthorchis viverrini*](https://en.wikipedia.org/wiki/Opisthorchis_viverrini) and [*Clonorchis sinensis*](https://en.wikipedia.org/wiki/Clonorchis_sinensis) ([cholangiocarcinoma](https://en.wikipedia.org/wiki/Cholangiocarcinoma)).

**Radiation**

Radiation exposure such as [ultraviolet radiation](https://en.wikipedia.org/wiki/Ultraviolet_radiation) and radioactive material is a risk factor for cancer. Many [non-melanoma skin cancers](https://en.wikipedia.org/wiki/Non-melanoma_skin_cancer) are due to ultraviolet radiation, mostly from sunlight. Sources of ionizing radiation include [medical imaging](https://en.wikipedia.org/wiki/Medical_imaging) and [radon](https://en.wikipedia.org/wiki/Radon) gas.

Ionizing radiation is not a particularly strong [mutagen](https://en.wikipedia.org/wiki/Mutagen). Residential exposure to [radon](https://en.wikipedia.org/wiki/Radon) gas, for example, has similar cancer risks as [passive smoking](https://en.wikipedia.org/wiki/Passive_smoking). Radiation is a more potent source of cancer when combined with other cancer-causing agents, such as radon plus tobacco smoke. Radiation can cause cancer in most parts of the body, in all animals and at any age. Children are twice as likely to develop radiation-induced leukemia as adults; radiation exposure before birth has ten times the effect.

Medical use of ionizing radiation is a small but growing source of radiation-induced cancers. Ionizing radiation may be used to treat other cancers, but this may, in some cases, induce a second form of cancer. It is also used in some kinds of [medical imaging](https://en.wikipedia.org/wiki/Medical_imaging).

Prolonged exposure to [ultraviolet radiation](https://en.wikipedia.org/wiki/Ultraviolet_radiation) from the [sun](https://en.wikipedia.org/wiki/Sun) can lead to [melanoma](https://en.wikipedia.org/wiki/Melanoma) and other skin malignancies. Clear evidence establishes ultraviolet radiation, especially the non-ionizing medium wave [UVB](https://en.wikipedia.org/wiki/UVB), as the cause of most non-melanoma [skin cancers](https://en.wikipedia.org/wiki/Skin_cancer), which are the most common forms of cancer in the world.

Non-ionizing [radio frequency](https://en.wikipedia.org/wiki/Radio_frequency) radiation from mobile phones, [electric power transmission](https://en.wikipedia.org/wiki/Electric_power_transmission) and other similar sources has been described as a [possible carcinogen](https://en.wikipedia.org/wiki/Possible_carcinogen) by the [World Health Organization](https://en.wikipedia.org/wiki/World_Health_Organization)'s [International Agency for Research on Cancer](https://en.wikipedia.org/wiki/International_Agency_for_Research_on_Cancer). Evidence, however, has not supported a concern. This includes that studies have not found a consistent link between mobile phone radiation and cancer risk.

**Heredity**

The vast majority of cancers are non-hereditary (sporadic). [Hereditary cancers](https://en.wikipedia.org/wiki/Hereditary_cancer) are primarily caused by an inherited genetic defect. Less than 0.3% of the population are carriers of a genetic mutation that has a large effect on cancer risk and these cause less than 3–10% of cancer. Some of these [syndromes](https://en.wikipedia.org/wiki/Syndrome) include: certain inherited mutations in the genes [*BRCA1*](https://en.wikipedia.org/wiki/BRCA1) and [*BRCA2*](https://en.wikipedia.org/wiki/BRCA2) with a more than 75% risk of breast cancer and [ovarian cancer](https://en.wikipedia.org/wiki/Ovarian_cancer), and [hereditary nonpolyposis colorectal cancer](https://en.wikipedia.org/wiki/Hereditary_nonpolyposis_colorectal_cancer) (HNPCC or Lynch syndrome), which is present in about 3% of people with [colorectal cancer](https://en.wikipedia.org/wiki/Colorectal_cancer), among others.

Statistically for cancers causing most mortality, the [relative risk](https://en.wikipedia.org/wiki/Relative_risk) of developing [colorectal cancer](https://en.wikipedia.org/wiki/Colorectal_cancer) when a [first-degree relative](https://en.wikipedia.org/wiki/First-degree_relative) (parent, sibling or child) has been diagnosed with it is about 2. The corresponding relative risk is 1.5 for [lung cancer](https://en.wikipedia.org/wiki/Lung_cancer), and 1.9 for [prostate cancer](https://en.wikipedia.org/wiki/Prostate_cancer). For [breast cancer](https://en.wikipedia.org/wiki/Breast_cancer), the relative risk is 1.8 with a first-degree relative having developed it at 50 years of age or older, and 3.3 when the relative developed it when being younger than 50 years of age.

Taller people have an increased risk of cancer because they have more cells than shorter people. Since height is genetically determined to a large extent, taller people have a heritable increase of cancer risk.

**Physical agents**

Some substances cause cancer primarily through their physical, rather than chemical, effects. A prominent example of this is prolonged exposure to [asbestos](https://en.wikipedia.org/wiki/Asbestos), naturally occurring mineral fibers that are a major cause of [mesothelioma](https://en.wikipedia.org/wiki/Mesothelioma) (cancer of the [serous membrane](https://en.wikipedia.org/wiki/Serous_membrane)) usually the serous membrane surrounding the lungs. Other substances in this category, including both naturally occurring and synthetic asbestos-like fibers, such as [wollastonite](https://en.wikipedia.org/wiki/Wollastonite%22%20%5Co%20%22Wollastonite), [attapulgite](https://en.wikipedia.org/wiki/Attapulgite), [glass wool](https://en.wikipedia.org/wiki/Glass_wool) and [rock wool](https://en.wikipedia.org/wiki/Rock_wool), are believed to have similar effects. Non-fibrous particulate materials that cause cancer include powdered metallic [cobalt](https://en.wikipedia.org/wiki/Cobalt) and [nickel](https://en.wikipedia.org/wiki/Nickel) and [crystalline silica](https://en.wikipedia.org/wiki/Crystalline_silica) ([quartz](https://en.wikipedia.org/wiki/Quartz), [cristobalite](https://en.wikipedia.org/wiki/Cristobalite) and [tridymite](https://en.wikipedia.org/wiki/Tridymite)). Usually, physical carcinogens must get inside the body (such as through inhalation) and require years of exposure to produce cancer.

Physical trauma resulting in cancer is relatively rare. Claims that breaking bones resulted in bone cancer, for example, have not been proven. Similarly, physical trauma is not accepted as a cause for cervical cancer, breast cancer or brain cancer. One accepted source is frequent, long-term application of hot objects to the body. It is possible that repeated burns on the same part of the body, such as those produced by [kanger](https://en.wikipedia.org/wiki/Kanger%22%20%5Co%20%22Kanger) and kairo heaters (charcoal [hand warmers](https://en.wikipedia.org/wiki/Hand_warmer)), may produce skin cancer, especially if carcinogenic chemicals are also present. Frequent consumption of scalding hot tea may produce esophageal cancer. Generally, it is believed that cancer arises, or a pre-existing cancer is encouraged, during the process of healing, rather than directly by the trauma. However, repeated injuries to the same tissues might promote excessive cell proliferation, which could then increase the odds of a cancerous mutation.

Chronic [inflammation](https://en.wikipedia.org/wiki/Inflammation) has been hypothesized to directly cause mutation. Inflammation can contribute to proliferation, survival, angiogenesis and migration of cancer cells by influencing the [tumor microenvironment](https://en.wikipedia.org/wiki/Tumor_microenvironment). [Oncogenes](https://en.wikipedia.org/wiki/Oncogene) build up an inflammatory pro-tumorigenic microenvironment.

**Hormones**

Some [hormones](https://en.wikipedia.org/wiki/Hormone) play a role in the development of cancer by promoting [cell proliferation](https://en.wikipedia.org/wiki/Cell_growth). [Insulin-like growth factors](https://en.wikipedia.org/wiki/Insulin-like_growth_factor) and their binding proteins play a key role in cancer cell proliferation, differentiation and [apoptosis](https://en.wikipedia.org/wiki/Apoptosis), suggesting possible involvement in carcinogenesis.

Hormones are important agents in sex-related cancers, such as cancer of the breast, [endometrium](https://en.wikipedia.org/wiki/Endometrium), prostate, ovary and [testis](https://en.wikipedia.org/wiki/Testicle) and also of [thyroid cancer](https://en.wikipedia.org/wiki/Thyroid_cancer) and [bone cancer](https://en.wikipedia.org/wiki/Bone_cancer). For example, the daughters of women who have breast cancer have significantly higher levels of [estrogen](https://en.wikipedia.org/wiki/Estrogen) and [progesterone](https://en.wikipedia.org/wiki/Progesterone) than the daughters of women without breast cancer. These higher hormone levels may explain their higher risk of breast cancer, even in the absence of a breast-cancer gene. Similarly, men of African ancestry have significantly higher levels of [testosterone](https://en.wikipedia.org/wiki/Testosterone) than men of European ancestry and have a correspondingly higher level of prostate cancer. Men of Asian ancestry, with the lowest levels of testosterone-activating [androstanediol glucuronide](https://en.wikipedia.org/wiki/Androstanediol_glucuronide%22%20%5Co%20%22Androstanediol%20glucuronide), have the lowest levels of prostate cancer.[[78]](https://en.wikipedia.org/wiki/Cancer#cite_note-Henderson-78)

Other factors are relevant: obese people have higher levels of some hormones associated with cancer and a higher rate of those cancers. Women who take [hormone replacement therapy](https://en.wikipedia.org/wiki/Hormone_replacement_therapy_%28menopause%29) have a higher risk of developing cancers associated with those hormones. On the other hand, people who exercise far more than average have lower levels of these hormones and lower risk of cancer. [Osteosarcoma](https://en.wikipedia.org/wiki/Osteosarcoma) may be promoted by [growth hormones](https://en.wikipedia.org/wiki/Growth_hormone). Some treatments and prevention approaches leverage this cause by artificially reducing hormone levels and thus discouraging hormone-sensitive cancers.

**Autoimmune diseases**

There is an association between [celiac disease](https://en.wikipedia.org/wiki/Celiac_disease) and an increased risk of all cancers. People with untreated celiac disease have a higher risk, but this risk decreases with time after diagnosis and strict treatment, probably due to the adoption of a [gluten-free diet](https://en.wikipedia.org/wiki/Gluten-free_diet), which seems to have a protective role against development of malignancy in people with celiac disease. However, the delay in diagnosis and initiation of a gluten-free diet seems to increase the risk of malignancies. Rates of gastrointestinal cancers are increased in people with [Crohn's disease](https://en.wikipedia.org/wiki/Crohn%27s_disease) and [ulcerative colitis](https://en.wikipedia.org/wiki/Ulcerative_colitis), due to chronic inflammation. Also, [immunomodulators](https://en.wikipedia.org/wiki/Immunotherapy) and [biologic agents](https://en.wikipedia.org/wiki/Biological_therapy_for_inflammatory_bowel_disease) used to treat these diseases may promote developing extra-intestinal malignancies.

**CELLULAR BASIS OF CARCINOGENESIS**

Cancer is a disease of uncontrolled growth and proliferation whereby cells have escaped the body’s normal growth control mechanisms and have gained the ability to divide indefinitely. It is a multi-step process that requires the accumulation of many genetic changes over time (Figure 1). These genetic alterations involve activation of proto-oncogenes to oncogenes, deregulation of tumour suppressor genes and DNA repair genes and ‘immortalisation’ which will be discussed in this chapter.



**Figure 1: Overview of the road to cancer.**

**Cell cycle regulation and the importance of apoptosis**

In normal cells, proliferation and progression through the cell cycle is strictly regulated by groups of proteins that interact with each other in a specific sequence of events. Checkpoints ascertain that individual stages of the cell cycle are completed correctly and ensure that incompletely replicated DNA is not passed onto daughter cells. Core to this control system are cyclin-dependent kinases (CDKs). CDKs are ‘master protein kinases’ that drive progression through the different phases of the cell cycle by phosphorylating and activating other downstream kinases. CDK activity is dependent on the presence of activating subunits called cyclins which are synthesised and degraded in a cell cycle-dependent manner. Cyclin-CDK complexes are further tightly regulated by CDK inhibitors.



**Figure 2: Cyclins and cyclin-dependent kinases (CDKs) regulate the cell cycle.**

The re-entry of cells into the cell cycle is decided at the **restriction point (R point)**. This decision is influenced by extracellular mitogenic signals which are transmitted via signalling pathways to key regulatory proteins, such as transcription factors (e.g. E2F) in the nucleus (refer to Figure 3, Section 2). These regulatory proteins ultimately activate the S-phase CDKs, which trigger the start of DNA synthesis.

In normal cells, activation of another transcription factor, p53, often referred to as the ‘guardian of the genome’, can impose cell cycle arrest and induce apoptosis (programmed cell death) through its ability to:

* induce the expression of cell cycle inhibitors to prevent proliferation of a cell until any damage has been repaired or
* initiate apoptosis, if the genomic damage is too great and cannot be repaired.

In >50% of all human tumours the p53 pathway is aberrant. Inactivation of the p53 protein renders it unable to signal and activate the cell’s apoptotic machinery resulting in increased survival of cancer cells.

**Cell immortalisation and tumourigenesis**

Immortalisation is defined as the acquisition of an infinite lifespan. Normal mammalian **somatic** cells proliferate a limited number of times before undergoing senescence. Senescent cells may remain metabolically active even though they have permanently ceased proliferation. Immortalisation is an essential step in the malignant transformation of normal cells and can be attributed, in part, to the presence of **telomerase**, the enzyme responsible for maintaining telomeres at the ends of chromosomes. By extending telomeric DNA, telomerase is able to counter the progressive telomere shortening that would otherwise lead to cell death. Unlike normal cells that lack detectable levels of telomerase activity, approximately 90% of human tumours consist of cells that contain an active telomerase enzyme.

CELL SIGNALLING IN CARCINOGENESIS

**Growth factors and their receptors**

Growth factors (GFs) play an important physiological role in the normal process of growth control aimed at maintaining tissue homeostasis. They transmit growth signals from one cell to another. These signals are sensed on the cell surface by specific growth factor receptors (GFRs). GFRs transfer the growth signal via signalling pathways to activate target molecules that promote proliferation.



**Figure 3: The MAP kinase pathway as an example of a growth signalling pathway.**

Steps that characterise normal cell proliferation include:

* the binding of a GF to its specific receptor on the cell membrane
* transient and limited activation of the GFR, which, activates several signal-transducing proteins (e.g. Ras) on the inner leaflet of the plasma membrane
* transmission of the signal by signal transduction molecules, either to cytosolic targets or to the nucleus where they activate transcription of specific genes
* entry of the cell into the cell cycle, ultimately resulting in cell division.

This pathway is often derailed in cancer and allows wayward cells to generate their own internal signals that stimulate proliferation and become independent of their environments. Cancer cells are able to induce their own growth stimulatory signals when mutations in the GFR gene occur, which facilitates activation in the absence of GFs or when overproduction of GFs results in an autocrine signalling loop.

**Other elements of cell signalling**

An alternative strategy by which cancer cells can become GF independent involves constitutive activation of internal signalling components. For example, the Ras protein in normal cells is switched off and does not signal unless a GFR becomes activated, which through a series of intermediaries, is able to activate the Ras protein, converting it from its quiescent state to an active, signal-emitting state. Thereafter, the Ras protein is able to release further downstream signals that are capable of inducing proliferation. In cancer cells, this signalling pathway is deregulated because structurally altered Ras proteins are able to continuously send growth stimulatory signals into the interior of the cell in the absence of GFs.

**Genes frequently mutated in cancer**

The genes that have been implicated in carcinogenesis are divided into two broad categories oncogenes (‘cell accelerators’) and tumour suppressor genes (‘cell brakes’) but also include DNA repair genes.

**Cellular oncogenes**

Genes that promote autonomous cell growth in cancer cells are called **oncogenes**, and their normal cellular counterparts are called **proto-oncogenes**. Proto-oncogenes are physiologic regulators of cell proliferation and differentiation while oncogenes are characterised by the ability to promote cell growth in the absence of normal mitogenic signals. Their products, oncoproteins, resemble the normal products of proto-oncogenes with the exception that oncoproteins are devoid of important regulatory elements. Their production in the transformed cells becomes constitutive, that is, not dependent on growth factors or other external signals. Proto-oncogenes can be converted to oncogenes by several mechanisms including point mutation and gene amplification resulting in:

* Overproduction of growth factors
* Flooding of the cell with replication signals
* Uncontrolled stimulation in the intermediary pathways
* Cell growth by elevated levels of transcription factors

**The RAS oncogene** is the most frequently mutated oncogene in human cancer. It encodes a GTP-binding protein Ras that functions as an on-off ‘switch’ for a number of key signalling pathways controlling cellular proliferation. In a normal cell, Ras is transiently activated and recruits Raf, to activate the MAP-kinase pathway to transmit growth-promoting signals to the nucleus. The mutant Ras protein is permanently activated leading to continuous stimulation of cells without any external trigger.

**Tumour suppressor genes**

Tumour suppressor genes encode proteins that are:

* receptors for secreted hormones that function to inhibit cell proliferation
* negative regulators of cell cycle entry or progression
* negative regulators of growth signalling pathways (e.g. APC or PTEN)
* checkpoint-control proteins that arrest the cell cycle if DNA is damaged or chromosomes are abnormal
* proteins that promote apoptosis DNA repair enzymes.

The transformation of a normal cell to a cancer cell is accompanied by the loss of function of one or more tumour suppressor genes and both gene copies must be defective in order to promote tumour development