

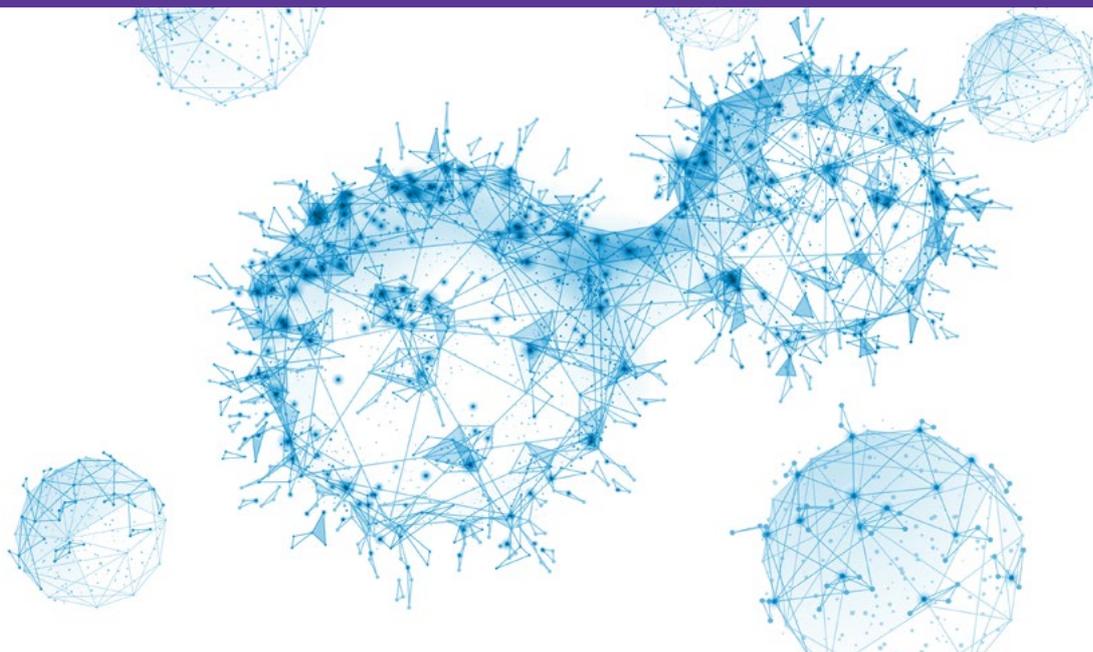
World
Cancer
Research
Fund



American
Institute for
Cancer
Research

CUP Continuous
Update
Project

Analysing research on cancer
prevention and survival



The cancer process

2018

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WORLD CANCER RESEARCH FUND NETWORK

Our Vision

We want to live in a world where no one develops a preventable cancer.

Our Mission

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

Our Network

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.

Our Continuous Update Project (CUP)

The Continuous Update Project (CUP) is World Cancer Research Fund Network's ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP's unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network's Cancer Prevention Recommendations (see inside back cover).

Through this process the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of World Cancer Research Fund Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. [The cancer process](#) is one of many parts that make up the CUP Third Expert Report: for a full list of contents see dietandcancerreport.org

The CUP is led and managed by World Cancer Research Fund International in partnership with the American Institute for Cancer Research, on behalf of World Cancer Research Fund UK, Wereld Kanker Onderzoek Fonds and World Cancer Research Fund HK.

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Key

References to other parts of the Third Expert Report are highlighted in [purple](#).

1. Basic concepts

This chapter summarises the wealth of evidence on how foods, constituents of foods, nutrition (including body composition) and physical activity can influence the biological processes that underpin the development and progression of cancer.

There are over 100 types of cancer, arising from different tissues. Even tumours arising from the same tissue are now recognised as comprising several subtypes, and as technology improves, the classification of subtypes is likely to expand even further. The different behaviours of each of these subtypes are only now beginning to be explored, and their relationships with nutritional factors and physical activity are not yet fully elucidated. Nevertheless, much is already known about the impact of diet, nutrition and physical activity on the cancer process.

What characterises cancer is a shared constellation of abnormal cell behaviours (see **Section 1.2**).

In order for cells, tissues and a whole organism to function normally, an adequate supply of energy and nutrients is needed throughout life. This allows the organism to grow and develop according to the template contained in the genetic code, so the organism has a normal structure and functional capacity, reflected in normal metabolism maintained through systems of regulation and control.

An adequate supply of energy and nutrients also allows an organism to have a functional reserve, which provides resilience against the inevitable challenges that any organism is bound to meet, either from within the body or from the external environment.

Imbalances in nutrition can have an impact on many of the processes that are involved

in maintaining normal structure and function, and cancer is one consequence. To understand how cancer develops, it is important to know first how cells function and how the body develops and functions normally (see **Box 1**).

Box 1: Nutrition

Nutrition is the set of integrated processes by which cells, tissues, organs and the whole body acquire the energy and nutrients for normal structure and function. This is achieved at the whole-body level through dietary supply and the body's capacity to transform the substrates and cofactors necessary for metabolism. All of these domains (diet, metabolic capacity, body composition and level of demand for energy and nutrients) are influenced by levels of physical activity and can vary according to different physiological, pathological or disease states.

1.1 Normal growth and development

1.1.1 Cells and tissues

Humans are complex organisms comprising multiple systems, which involve anatomically distinct organs (such as the heart, lungs, liver and brain) as well as less clearly demarcated components (such as blood, fatty tissue and fluid). These systems continually interact to ensure the organism can grow, develop and function normally.

Each organ has unique functions, reflected in its different tissues, with each type of tissue being composed of cells with a particular range of functions, which are specific to that tissue and define its role in the body. Some systems, such as the immune system, are not confined to a particular organ and have cells that are widely distributed among the tissues of the body but, nevertheless, retain their own recognisable form and function.

This wide variety of different types of cells, tissues and organs arises from just a single fertilised egg, which undergoes a highly regulated series of cell divisions. As the organism develops, cells acquire the capability to perform their specialised functions, generally accompanied by a characteristic appearance.

This process of specialisation is called differentiation. It explains why different organs and tissues look different not only to the naked eye but also at the microscopic and molecular levels. In mature, healthy human cells, the process of differentiation is normally irreversible, meaning a cell's specialism becomes fixed.

Adult humans typically have about 10^{13} – that is ten trillion – cells working in harmony with each other. Naturally, the number of cells in each organ and in the body as a whole increases during growth; but even during adulthood cells replicate, divide and die off at a rate that, though varying between different tissues, maintains the integrity of all tissues.

The cells that make up tissues are constantly renewed, and aged cells that can no longer function normally are removed. This cellular turnover is fed by a number of cells in each tissue called stem cells, which retain the ability to differentiate into a range of mature types of cell.

As cells age, they become more likely to function abnormally. Each cell has a programme that recognises when it has reached the end of its useful life, for example, if it is damaged. When this programme is activated, the cell effectively commits suicide. This process is called apoptosis and is critical for keeping tissues healthy and functioning normally.

1.1.2 Cell structure and biology

The vast majority of mammalian cells have a typical structure comprising a plasma membrane, cytoplasm and a nucleus. The composition and function of these components is determined by the genetic code contained within the nucleus, the developmental stage of the organism, the immediate microenvironment in which the cell exists and the external factors to which the organism is exposed.

1.1.2.1 Plasma membrane

The plasma membrane is a lipid bilayer, which has proteins embedded in or attached to it. The membrane separates the inside of the cell (the intracellular environment containing the cytoplasm and nucleus) from the outside (extracellular) environment. It controls the entry and exit of metabolites and nutrients, and enables the cell to sense its external and internal environment to enable proper functioning of the cell and its interactions with its surroundings.

Specific functions of membrane proteins include the following:

- they help form cell junctions, which are essential in tissue organisation and function
- they act as enzymes with catalytic functions to ensure effective metabolism
- they enable active or passive transport of ions and molecules in and out of the cell, to maintain optimal metabolic functioning

- they act as cell-to-cell recognition molecules for both homotypic and heterotypic cell interactions
- they act as anchorage proteins for adhesion to the extracellular matrix
- they act as receptors, which sense the presence of molecules (ligands) for signal transduction from systemic (endocrine), local (paracrine), cell autonomous (autocrine) and intracrine (within a given cell) origin.

1.1.2.2 Cytoplasm

The cytoplasm comprises everything that is within the plasma membrane apart from the nucleus. There are many organelles (membrane-bound structures with specific cellular functions) within the cytoplasm, such as mitochondria, which are responsible for cellular energy metabolism, and ribosomes, where proteins are synthesised. In addition, the cytoplasm contains the cytoskeleton, which is essential for maintaining cell shape, for cell motility and division, and for organelle movement.

Many critical cellular functions such as energy production, protein synthesis and metabolism occur within the cytoplasm and its organelles.

1.1.2.3 Nucleus

The nucleus contains the genetic material of each cell (though some specialised cell types, such as red blood cells, lack a nucleus and genetic material). The genetic material, which contains the programme for the development of cells, tissues, organs and the whole organism, takes the form of genes, which are contained in stretches of DNA (deoxyribonucleic acid).

DNA is a macromolecule (large molecule) comprising two long chains, both made of repeating units called nucleotides. Each nucleotide consists of three parts:

a deoxyribose sugar and a phosphate group, which together form the backbone of each DNA chain, and one of four possible bases (called adenine, cytosine, thymine and guanosine), which projects from the DNA chain. The two chains are organised into a double spiral or helix, with adenine on one chain always being paired with thymine on the other, and cytosine on one chain being paired with guanine on the other. The two chains are said to be complementary because of this pattern in the base pairing.

The two long chains of DNA are packed around protein cores called histones to form a complex called chromatin; in turn these complexes are tightly coiled into structures called chromosomes. Human cells have 23 pairs of chromosomes, with each chromosome being made up of a single molecule of DNA.

The order of the nucleotides within DNA makes up the genetic code. Individual genes are transcribed to form a molecule called messenger ribonucleic acid (mRNA) in the nucleus. The mRNA is then exported to the cytoplasm, where it binds to organelles called ribosomes. Ribosomes translate the mRNA – assembling amino acids into proteins, with the sequence of amino acids in the protein being defined by the order of nucleotides in the mRNA. (In addition to the nuclear DNA, the mitochondrion also contains its own DNA, which encodes proteins necessary for cellular energy metabolism.)

All of the cells in any individual carry the same genetic code in their DNA, but the different range of capabilities that the cells manifest depends on a regulated series of events (see **Section 1.1.6**) that determine which particular parts of the genetic code are active at any particular time in any specific tissue.

Normal early development, from fertilisation through embryogenesis and fetal life, features a symphony of coordinated processes, which

involve switching genes on and off in a highly predictable and regulated way that varies over time and between different tissues as well as different cells within tissues. The genetic code is therefore a template that provides the opportunity for achieving full genetic potential and the necessary complexity acquired during growth and development across all organs and systems, from fetal life in the womb, through infancy, childhood and adulthood.

1.1.3 Normal cell cycle

The cell cycle is the highly regulated process – remarkably similar across all living cells – by which cells divide, allowing tissues to grow and remain healthy. Growth and maintenance of healthy tissue requires cells to create identical copies of themselves as they mature and age. This means that a cell's chromosomes, including their DNA, must be replicated and then separated into two daughter cells, each with its own complete set of chromosomes.

The cell cycle has been meticulously described and has several clearly defined stages, corresponding to preparation for DNA replication and cell division into two daughter cells. However, most cells are in a resting phase for much of the time, between periods of active cell division.

Every time a cell divides, it replicates its DNA (and therefore its genetic code) so that each daughter cell has identical copies to the parent. Before a cell divides, the two, complementary, opposing strands of each DNA double helix separate and are then replicated, so each daughter cell has a new double strand. (An exception is germ cells, which make sperm and eggs, as they divide in a different way.)

DNA replication is a complex process and is vulnerable to the introduction of errors in copying the sequence of nucleotides. In addition, cells are constantly exposed

to factors that can damage DNA at any time, either agents from the environment outside the body (exogenous), such as radiation or chemicals in cigarette smoke; or agents generated by processes that occur within the body (endogenous), such as free radicals or other by-products of metabolism.

Normal progression through the cell cycle is monitored at checkpoints that sense, for example, errors in DNA replication and chromosome segregation, and DNA damage caused by endogenous factors or exogenous agents. Activation of these checkpoints stops the cell cycle, allowing cells to repair any defects and prevent their transmission to daughter cells. There are a number of processes that can detect particular types of DNA damage and repair them.

If repair is unsuccessful, owing either to defects in the machinery for detecting or repairing damage to DNA, or because the systems are overwhelmed by an external agent or other endogenous challenge (see **Section 2.2**), cells may undergo apoptosis. This protects the tissues from accumulating cells with damaged DNA.

The processes involved in repairing DNA are not perfect. Cells that have abnormal DNA may be produced – permanent changes in the DNA sequence are called mutations.

1.1.4 Mutations

Failure of a cell to copy its DNA accurately during the cell cycle, or to repair damage to DNA, may result in a permanent change in the DNA sequence called a mutation. Mutations can vary in size from an alteration in a single nucleotide to changes in whole segments of chromosomes. Some mutations may have potentially beneficial effects – this underpins the possibility of evolution by natural selection – and others may be neutral or harmful.

Mutations may lead to failure of a gene to produce a protein, or to the production of a protein that functions abnormally or not at all.

Accumulation of DNA alterations in surviving daughter cells may also result in genomic instability – meaning cells are more susceptible to accumulating the genetic changes needed to form a cancer cell. Many external cancer-causing agents operate by causing mutations.

1.1.5 Genetic polymorphisms

The most common inherited variations in the nucleotide sequence of DNA (occurring in more than one in every 100 people) are called single nucleotide polymorphisms (SNPs). These variations in the DNA sequence are responsible for many of the genetic differences between individuals. The association of common genetic variants such as SNPs with cancer has been an area of intense research over the past decades.

Genome-wide association studies (GWAS), which evaluate thousands of variants across the genome simultaneously, have led to the discovery of hundreds of variants linked to cancer and have improved understanding of the many different genetic abnormalities that can lead to cancer development. Nevertheless, much remains to be discovered regarding the contribution of genetic polymorphisms to the cancer process, as well as the interaction between such genetic variants and environmental exposures.

1.1.6 Cell differentiation and gene expression

Human cells contain approximately 20,000 to 25,000 genes; however, these genes account for only 1 to 1.5 per cent of the entire DNA in a cell. The remainder of the DNA comprises sequences of nucleotides that are responsible for controlling how the genes work, and how they are transcribed and regulated, as well as large amounts of DNA whose function has not yet been characterised.

Although all cells in an organism contain the same genetic code in their DNA, and therefore the same set of genes, the cells in different tissues look and behave differently because each type of cell has a different set of functioning genes. Different combinations of genes are expressed (turned on) in different types of cells.

Gene expression is the process by which the information encoded in the DNA of a gene is transcribed and translated to form a functional gene product, typically a protein. Several mechanisms are known to influence whether any particular gene is switched on or off, and it is these processes that determine how a cell behaves.

Some sets of genes – those called ‘housekeeping’ genes – are expressed by almost all cell types. These genes generally encode proteins that participate in basic cell functions such as metabolic pathways, and the synthesis and processing of DNA, RNA or proteins. Other genes have more restricted expression, being expressed only in specific cell types and/or at particular stages of development. The pattern of gene expression determines cells’ structure and function (phenotype).



The regulatory processes that control gene function are central to the normal development of the fertilised egg into an embryo, and then into a fetus, child and adult. Regulation of the process of switching the function of genes on or off in an organised way is critical to normal development and to the normal function of cells. As tissues mature, their cells do not display many of the functions that their ancestral cells demonstrated during development, even though the genetic programme responsible for such functions remains intact.

For instance, the ability of cells to promote the development of new blood vessels (to support tissue growth) and of cells to migrate within the developing embryo is integral to normal development, as is the ability of cells to divide rapidly and to colonise neighbouring tissues, but these are not typical functions of cells in mature tissues. They are, however, typical characteristics of cancer.

1.1.7 Transcription factors

One mechanism that controls gene expression involves a set of proteins called transcription factors, which bind to DNA and form part of the process that transmits information from the external cell environment or the cytoplasm to the nucleus. Transcription factors bind to specific regions of genes and have the effect of either promoting or suppressing gene expression.

1.1.8 Epigenetic regulation

Alterations in gene expression may also occur as a result of modifications in the structure of DNA and chromatin known as epigenetic changes. Epigenetic changes are reversible, heritable modifications of the genome that alter gene expression without involving changes to the sequence of nucleotides in DNA.

Epigenetic regulation of gene expression is governed by several distinct biochemical

phenomena. One example is DNA methylation, which is the covalent addition of a methyl (CH₃) group to particular parts of the DNA called CpG islands. In healthy cells, methylation of DNA promoter regions assists in the appropriate regulation of gene expression. DNA methyltransferases are enzymes responsible for establishing and maintaining the normal methylation pattern.

Compared with healthy cells, malignant cells have abnormal DNA methylation patterns. Numerous genes can be hypermethylated (having increased levels of DNA methylation) in cancer, including genes involved in cell cycle regulation, as well as those associated with DNA repair, apoptosis and metastasis. On the other hand, global hypomethylation (decreased levels of DNA methylation overall) induces genomic instability, which also promotes cancer development.

Another form of epigenetic regulation is through modification of histone structure. The structure of histones can be altered either by methylation (like the structure of DNA) or, more commonly, by acetylation (addition of an acetyl group). Acetylation (or methylation) of histones tends to create a more open DNA structure, facilitating gene transcription into mRNA and subsequent translation of mRNA into protein (gene expression). Acetylation and deacetylation (removal of acetyl groups) are mediated by the enzymes histone acetyltransferase (HAT) and histone deacetylase (HDAC), respectively.

Yet other epigenetic modifications result from the activity of non-coding RNA molecules such as microRNAs. MicroRNAs are small RNA molecules, which do not code for proteins, and are emerging as key regulators of gene expression. They work by binding to protein-encoding mRNA, thereby affecting mRNA stability and translation. They may be involved in the regulation of over half of all genes expressed in mammalian cells. Indeed, a

single microRNA may alter the expression of hundreds of genes. The human genome encodes for over 1,000 microRNAs.

1.1.9 Cell signalling

Cells respond to external stimuli through a molecular mechanism known as cell signalling.

Cells within a tissue normally communicate with each other using a network of locally produced chemicals that can include cytokines, growth factors and hormones. These signals are critical for regulating fundamental cellular functions including proliferation, differentiation and apoptosis.

For example, cell proliferation is a tightly controlled and coordinated process, which is stimulated by growth factors, balanced against growth inhibitors. Growth factors bind to specific receptors on the cell surface and transmit a signal into the cell, which is relayed to the nucleus. In the nucleus, genes are switched on to produce the proteins necessary for cell division.

Transmission of the growth signal from outside the cell into the nucleus requires a series of steps. The shape of the receptor changes when the growth factor binds to it, which causes part of the receptor to become activated, often by a process called phosphorylation. A regulated process of phosphorylation and dephosphorylation is necessary for the appropriate initiation, transmission and cessation of signals. This may be influenced by the energy and nutritional environment that the cell is exposed to.

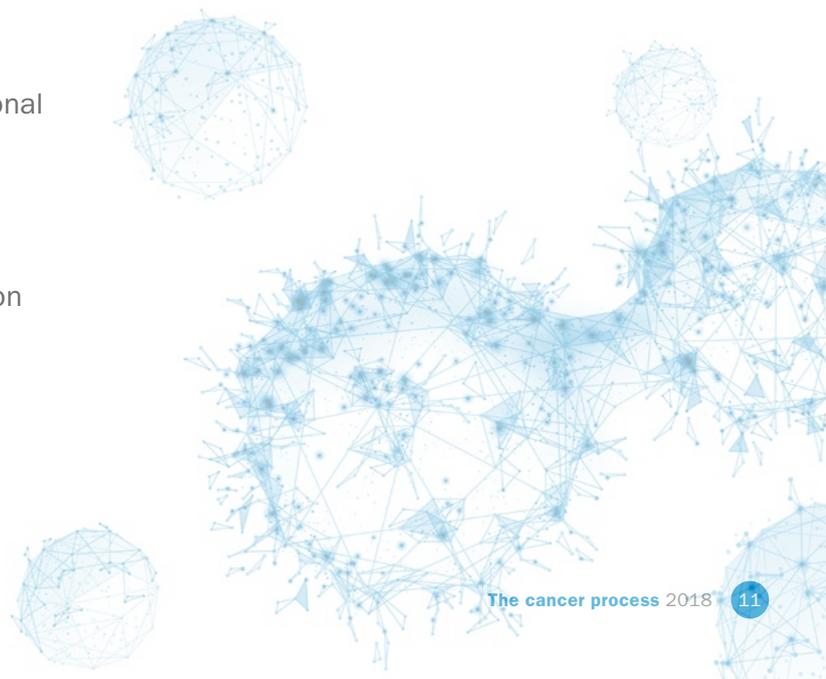
1.1.10 Growth, development and ageing

The process of development after fertilisation involves the transformation of energy and nutrients from the environment into an organism's differentiated tissues, through specific, regulated processes exquisitely coordinated through time. The result is

the acquisition of functional tissue and consequent functional capacity.

Although each cell and tissue perform their own functions, the capacity of the whole organism to withstand the environmental challenges that can be expected through life is a key overall marker of health. When external challenges exceed the capacity of the organism to endure them, there are adverse consequences for structure or function, which can be characterised as stress. A good nutritional state during development and maturation gives an organism the ability to withstand external challenges without stressing the whole system (resilience).

At the level of the whole body, ageing is associated with well-recognised structural changes, which are accompanied by or reflect functional loss – for example, reduced skin elasticity, bone strength and resilience. Ageing is characterised by a loss of reserve capacity and then by an actual loss of function, and a greater likelihood of stress and loss of homeostasis in the face of external challenges, such as infections. These whole-body effects reflect changes at a cellular or molecular level, including telomere shortening.



Telomeres are repetitive nucleotide sequences at the end of chromosomes that represent an internal biological clock. With each cell division, telomeres are shortened. When they become too short, the DNA strand becomes unstable and the cells become unviable.

Telomere length has been hypothesised to represent a marker of biological age as opposed to chronological age. Although telomeres become shorter with repeated cell divisions during the ageing process, other processes may also contribute to this shortening. For example, various types of cellular and tissue stress, as well as smoking, obesity, low levels of physical activity and a poor diet are all under study as potential modifiers of telomere length.

1.1.11 Normal development

Normal development after fertilisation requires the tissues of an embryo to behave in ways that are unique to that phase of life and to communicate with each other in a coordinated way through the processes of cell signalling. Cells divide especially rapidly and migrate from one part of the embryo to another. This involves forging new tissue within neighbouring tissues in a way that is not normally seen in more mature organisms, as well as promoting the growth of new blood vessels (angiogenesis) to support the new tissue.

These processes are highly coordinated through cell signalling and regulated under the control of transcription factors and epigenetics. Under normal circumstances, the genes that control these processes are suppressed once the developmental need has passed. However, although these genes normally become inactive, or latent, in an adult organism, they retain the potential to be activated.

Many of the abnormal characteristics of cancer cells are distorted versions of those of cells during embryogenesis: disordered

cell signalling, rapid cell division, migration through tissues, invasion of neighbouring tissue and angiogenesis. In many ways cancer can be seen as the inappropriate and abnormal resurrection of existing primitive pathways necessary for normal development after fertilisation.

1.1.12 Disordered nutrition during development

The generation of new cellular material and tissue during growth and development creates a demand for energy and for a particular balance of nutrients. Energy and nutrients are necessary, for example, to ensure that the enzymes that drive development can be synthesised and that they have the appropriate chemicals to function properly. In addition, the simple increase in the volume of tissue creates an obligatory demand for energy and nutrients.

If there is a limitation in the supply of energy or specific nutrients, then this can affect the process of cell division and differentiation, thereby affecting the health of the individual.

The various phases of development – from fertilisation through embryonic and fetal life, and throughout childhood to adult life – each create a distinct demand for energy and nutrients. Should the nutritional supply (either through the placenta or the diet) fail to meet demand either in quality or in quantity, then normal development will be compromised. Adaptive processes mediated through epigenetics are invoked to maintain critical functions such as brain development, but this may be at the expense of other developmental processes.

The consequences of such nutritional mismatch may include long-lasting structural and functional changes that can persist throughout life and may influence susceptibility to cancer or other diseases. The particular impact will depend on the nature and degree

of any nutritional inadequacy or imbalance, and its timing during development, growth and maturation, as well as the later environment. Such effects may explain, in part, the relationships between the risk of a number of cancers and markers of early life nutrition, growth and development, such as birthweight and height.

1.1.13 Nutrition, body composition and physical activity

From the moment of conception, the processes of life generate a demand for fuel. These processes include the generation of tissues during growth and for pregnancy, the metabolic processes involved in biochemical reactions, the maintenance of membrane integrity and of fluid and electrolyte balance, and mechanical work (for example, when breathing).

The fuel needed to sustain life includes energy (calories) as well as the chemical substances necessary to support these processes.

These substances include not only the basic chemical building blocks (substrates) of biochemical pathways, but also components of enzymes that drive or catalyse the biochemical reactions. Some enzymes need a particular substance – or cofactor – to function correctly. Cofactors are either a chemical element (such as iron, copper or selenium), or a biochemical compound, usually a vitamin (or derived from a vitamin). Together all of the life-sustaining biochemical reactions that take place in an organism are called metabolism.

In addition to the demands of basal metabolism (that is when an organism is at rest), any form of skeletal muscle activity adds a further demand for energy. Typically, in modern industrialised societies, about two thirds of the total energy demand is from basal metabolism and about a third is from physical activity. In the past, the ratio might have been nearer half and half, as greater amounts of physical activity were necessary for survival,



especially for finding, transporting and preparing food. However, the variation in total energy demand between modern humans may be much greater than that of their ancestors, since many people undertake physical labour that might exceed what was performed by humans historically.

Physical activity is any movement using skeletal muscle. It is more than just exercise, which is a particular type of physical activity. It also includes everyday activities such as standing, walking, domestic work and even fidgeting. The amount and type of physical activity can influence the body's overall metabolic state, as well as total requirements for energy, which in turn can impact the amount of food (and nutrients) that can be consumed without storing excess energy as fat.

Ultimately, all the energy, substrates and cofactors needed for metabolism (called nutrients) come from the diet. Most of the substrates for the biochemical reactions that make up metabolism can actually be synthesised by the body from various components of the diet. Energy cannot be manufactured. It is derived from fat, protein and carbohydrate (macronutrients), and alcohol in the diet.

Substrates and cofactors that cannot be synthesised by the body have to be consumed ready-made and are called essential nutrients. However, other nutrients, which do not have to be consumed ready-made in the diet, are also essential for normal metabolism (such as glucose) and the body's ability to make them is therefore critical. As well as vitamins (not all of which act as cofactors) and minerals (the chemical elements including trace elements needed as cofactors), some amino acids (the building blocks of proteins) and some types of fatty acid must also be consumed ready-made in the diet.

The diet also contains many substances that are not nutrients (that is, they are not necessary for metabolism) but can nevertheless influence metabolic processes. These include common chemicals such as caffeine and some harmful substances such as arsenic, as well as chemicals that are essential for plants but may also have biological effects in humans (phytochemicals) such as lycopene from tomatoes and isoflavones from soybeans.

In addition, the diet contains dietary fibre, the component of plant foods that is not fully digested in the small bowel and reaches the large bowel (colon), where it is fermented by bacteria. This fermentation process provides energy, some nutrients and other substances that are absorbed and can also have biological effects on the body. Dietary fibre may also have physiological effects through delaying gastric emptying, modulating glucose absorption and metabolism, and speeding up the transit of food through the digestive tract.

The processes of metabolism take place within an aqueous solution in the cells of the body. Water is therefore crucial for survival. The generation of energy from macronutrients in food is equally critical. Human evolution has ensured that robust processes regulate the intake both of water

and of macronutrients. Their distribution and concentration within tissues and cells is critical for normal function and is highly regulated under normal circumstances.

Excess energy intake that is not balanced by physical activity leads to positive energy balance and ultimately weight gain and greater body fatness.

1.2 Key cellular processes relevant for cancer

1.2.1 DNA damage and repair

As discussed in **Section 1.1.3**, each time a cell in the body divides into two new daughter cells, there is potential for errors in the replication of the DNA. Mutations in the DNA sequence may result in non-functioning genes or in the production of proteins with altered amino acid sequences, which can lead to changes in how cells function.

Furthermore, DNA is continuously exposed to products of normal intracellular metabolism, including reactive oxygen species, hydroxyl radicals and hydrogen peroxide; as well as to external environmental factors such as ultraviolet (UV) light and cigarette smoke, which can damage DNA, affecting its structure and integrity, at any time. The physiological responses to DNA damage can be modified by dietary factors and by the action of hormones, which in itself can depend on exposure to food, physical activity and excess body fatness.

Defects in DNA repair, including defects in telomere maintenance and in the DNA damage checkpoints that control progression through the cell cycle, lead to genomic instability [1], meaning there is a more rapid accumulation of deleterious DNA mutations and a predisposition to cancer and its progression. This genomic instability provides a way in which a healthy cell can accumulate sufficient mutations to become malignant [2].

However, as described in **Section 1.1.3**, the cell has several systems that protect against genomic instability, whether that instability is driven by the malfunctioning of cell cycle checkpoints, persistent DNA damage or telomere dysfunction.

The tumour-suppressor protein p53, which acts as a ‘guardian of the genome’, plays a central role in protecting cells against cancer, which is reflected in the finding that TP53 (the gene that encodes the p53 protein) is the most commonly mutated gene in human cancer.

In response to a range of stresses – including errors in DNA replication, other DNA damage, hypoxia or proliferative signals – p53 causes cells to undergo either cell-cycle arrest or apoptosis. Cell-cycle arrest is a checkpoint function that allows cells to pause in the cell cycle, either temporarily or permanently, to prevent the perpetuation of potentially oncogenic mutations [3]. Apoptosis is a process of ‘cell suicide’, which is invoked when cellular defects such as DNA damage are such that normal function is compromised [4]. Cells that are experiencing these stresses and that also lack properly functioning p53 proliferate or survive inappropriately, promoting the development of cancer.

Most cancers acquire genomic instability, which renders DNA and chromosomes susceptible to additional mutations and also includes chromosomal instability. Cancer cells accumulate mutations that promote uncontrolled proliferation, even in the absence of external signals, and defective responses to anti-proliferative signals. Taken together, unregulated proliferation and an increased susceptibility to accumulating mutations contribute to tumour progression, the acquisition of more aggressive tumour phenotypes and resistance to chemotherapeutic agents.

1.2.2 Tumour suppressor genes and oncogenes

Mutant genes associated with carcinogenesis are often categorised as tumour suppressor genes or oncogenes.

Tumour suppressor genes are critically important genes that encode proteins that typically slow cell proliferation, maintain differentiation, and edit and correct DNA damage, which is key to preventing the cell cycle from progressing when errors are detected and require repair. If these genes are inactivated (either by mutation or through epigenetics), then DNA damage is more likely to persist and cancer development is a greater possibility (hence the name ‘tumour suppressor genes’).

Oncogenes are abnormally functioning versions of genes that are typically involved in the activation of growth, replication and survival signals (such as hormones and tissue growth factors or their receptors, as well as the proteins involved in the intracellular signalling pathways that are linked to these agents), or less commonly, a normal gene expressed at inappropriately high levels, which is often the result of a mutation in the promoter/regulatory region of the gene. Under normal circumstances, cell proliferation is regulated by a balance between the action of a variety of proteins that together promote cell replication and the action of other factors that tend to reduce proliferation. If the genes that code for these proteins, or those responsible for other normal functions such as apoptosis, function abnormally (again through mutation or epigenetic change), then abnormal or unregulated proliferation of cells characteristic of cancer can occur. The abnormally functioning genes are therefore called oncogenes, while their normal counterparts are called proto-oncogenes.

Typically, oncogenes are viewed as dominant mutations, as the mutation results in a 'gain-of-function' protein, which causes unregulated proliferation and prolonged survival. In contrast, cancer-causing mutations in tumour suppressor genes are considered to be recessive mutations, containing a 'loss of function' mutation.

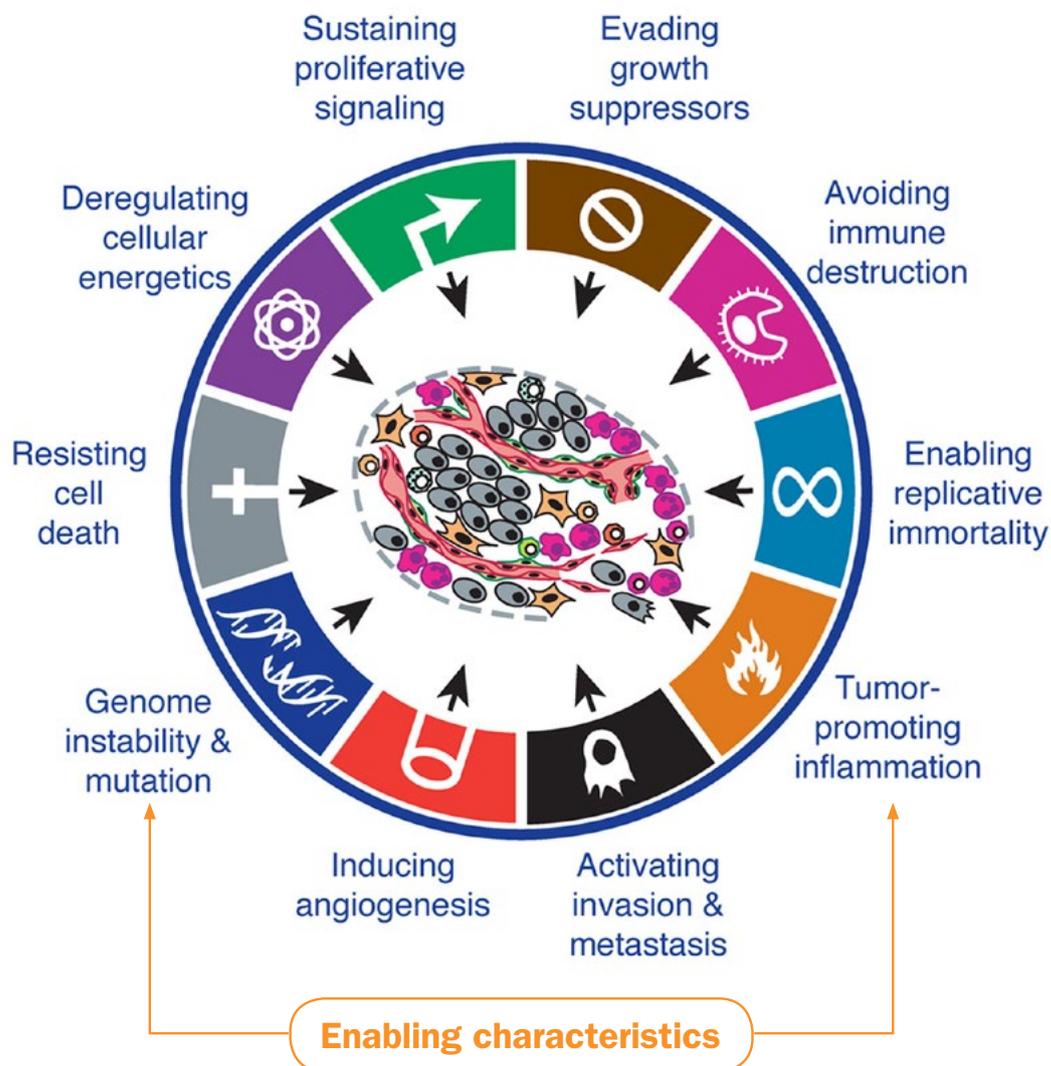
Each normal cell has two copies of the same gene. A mutation in just one copy is sufficient for activation of an oncogene to induce aberrant cancer behaviour.

Conversely, both copies must be damaged in order for the loss of function mutations of the tumour suppressor gene to have a carcinogenic impact.

1.2.3 Hallmarks of cancer

Cancer develops when the normal processes that regulate cell behaviour fail and a cell becomes the ancestor of a group of cells that share its functional abnormalities (see **Figure 1**). Errors in cell regulation generally result from mutations; more than one mutation

Figure 1: Hallmarks of cancer and two enabling characteristics



Adapted from: Cell 144, Hanahan D and Weinberg RA, Hallmarks of cancer: the next generation, 646–74, Copyright (2011), with permission from Elsevier.

Despite the multitude of pathways through which genetic damage can lead to the development of cancer, almost all solid tumours can be characterised by a relatively small number of phenotypic functional abnormalities. These eight hallmarks of cancer are facilitated by two enabling characteristics, genome instability and mutation, and tumour-promoting inflammation.

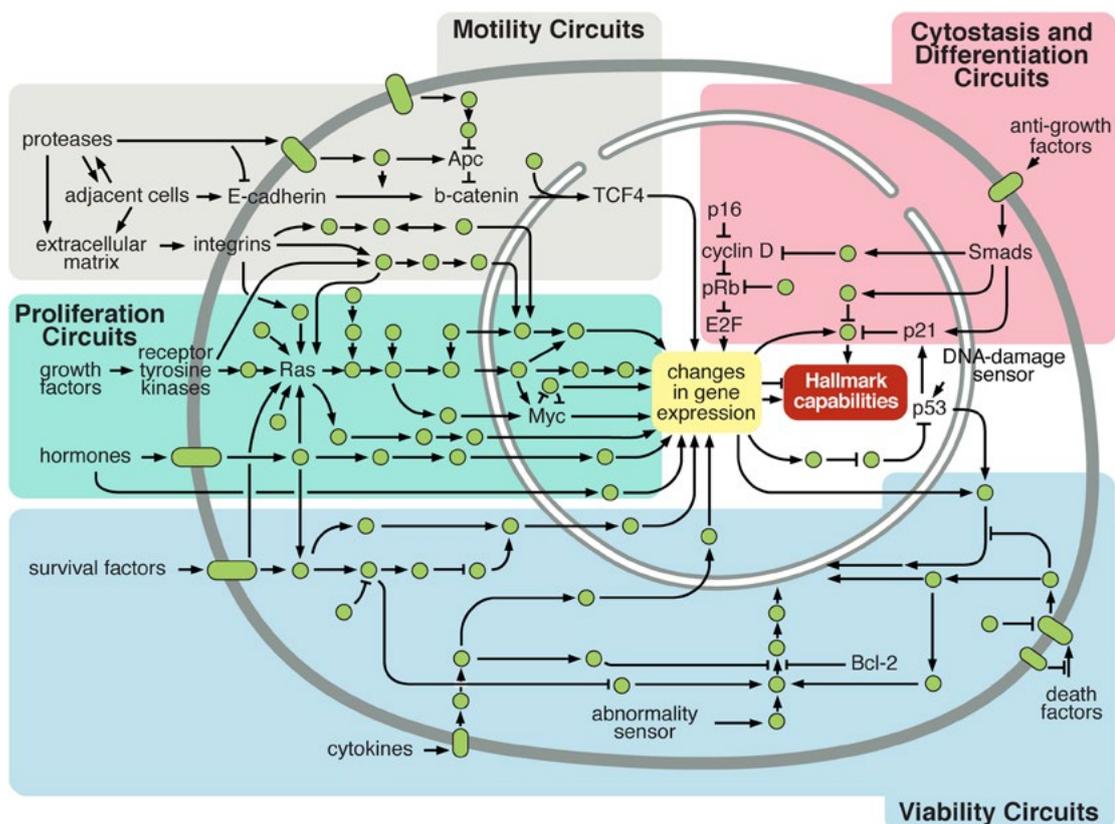
is generally required to lead to cancer. Much research is devoted to identifying the causes of the mutations that underpin the development of cancer.

Sometimes one of the mutations that contributes to the development of cancer is inherited. People with such inherited mutations are at high risk of developing cancers since they need to acquire fewer subsequent mutations.

Although such familial cancers are uncommon (inherited genetic mutations play a major role in only 5 to 10 per cent of all cancers [5]), it is important to identify them so that personalised preventive strategies can be offered to carriers and their families.

Most cancers, however, are not related to a single inherited mutation that substantially increases cancer risk, but result from the accumulation of genetic damage in cells over time. Over the last few years it has become clear that, despite the bewildering variety of possible mutations that can combine to promote cancer, most cancers display a much narrower range of functional changes. These phenotypical characteristics (as opposed to the genetic factors that can lead to them) have been termed the ‘hallmarks of cancer’ (see **Figure 2**).

Figure 2: Intracellular signaling networks regulate the operations of the cancer cell



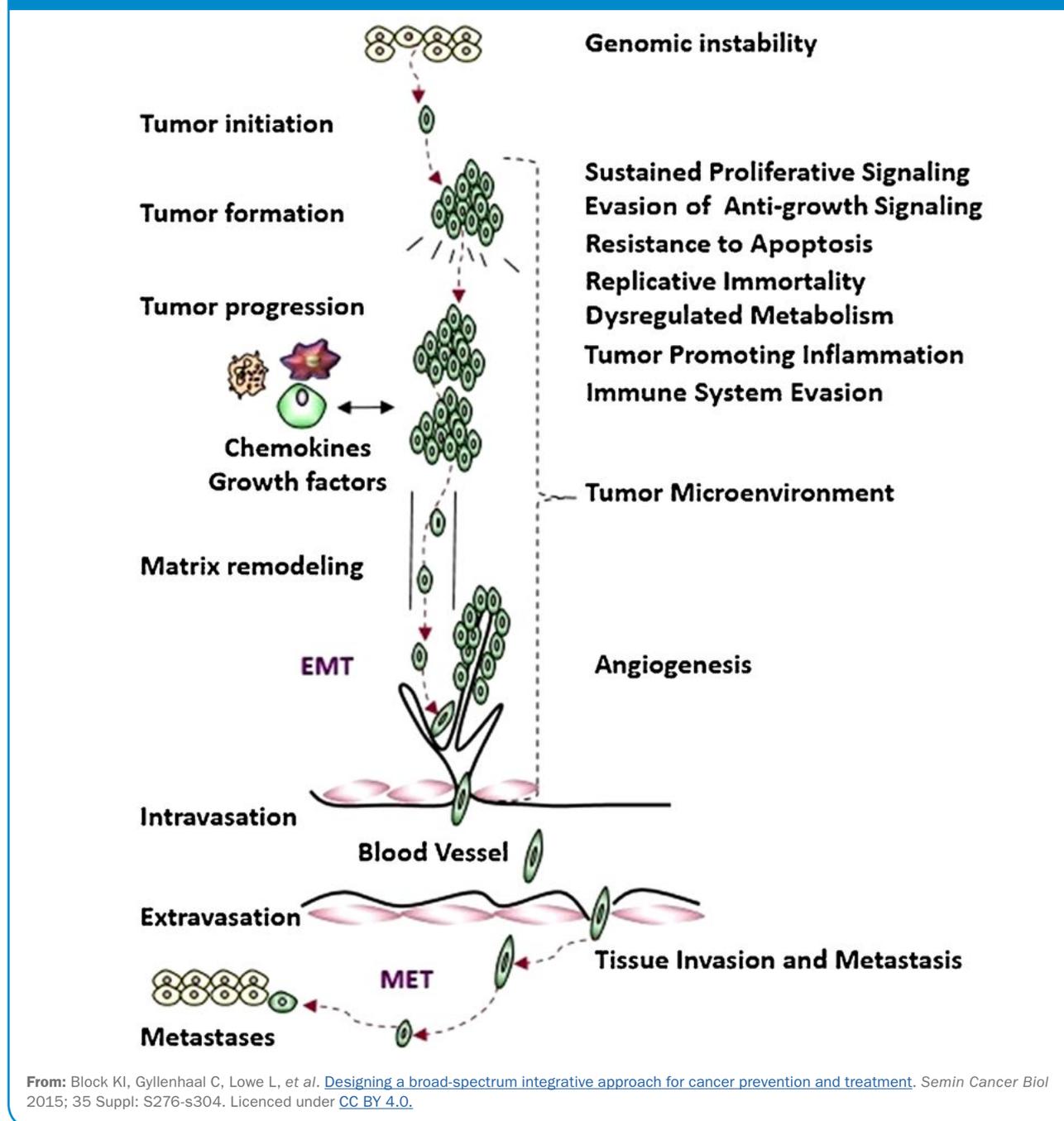
From: Cell 144, Hanahan D and Weinberg RA, Hallmarks of cancer: the next generation, 646–74, Copyright (2011), with permission from Elsevier.

An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate subcircuits, depicted here in differently coloured fields, are specialised to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such subcircuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these subcircuits is connected with signals originating from other cells in the tumour microenvironment.

The current model identifies eight phenotypical characteristics, which are all involved with disordered control of cell function, along with two more fundamental enabling characteristics (see **Figure 3**):

- Sustained proliferative signalling
- Resisting cell death
- Activating invasion and metastasis
- Inducing angiogenesis
- Evading growth suppressors
- Enabling replicative immortality
- Avoiding immune destruction
- Deregulating cellular energetics
- Enabling characteristic: genomic instability and mutation
- Enabling characteristic: tumour-promoting inflammation.

Figure 3: Stages of cancer development and the hallmarks of cancer



From: Block KI, Gyllenhaal C, Lowe L, et al. *Designing a broad-spectrum integrative approach for cancer prevention and treatment. Semin Cancer Biol* 2015; 35 Suppl: S276-s304. Licenced under [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/).

The hallmarks of cancer represented on the right are functional abnormalities characteristic of cancer cells, which can be related to the pathophysiological stages of cancer development, represented on the left.

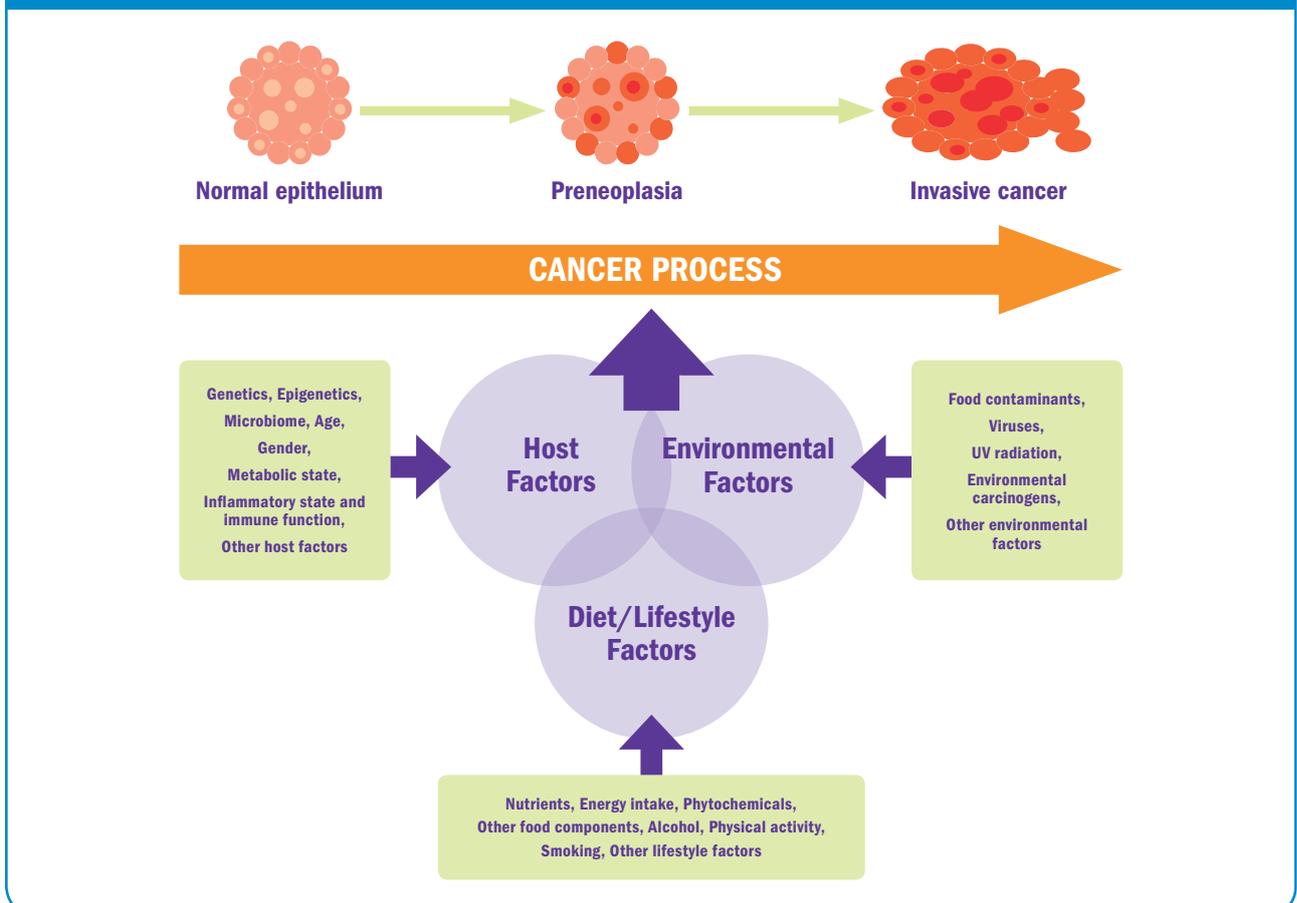
Nutritional factors and physical activity can have an impact on all of these phenotypic characteristics. This is the fundamental explanation of how foods, nutrition and physical activity influence the risk of developing cancer and its course once diagnosed. The impact of nutrition and physical activity on these hallmarks of cancer is the subject of **Section 2**.

1.3 Established causes of cancer

The factors that compromise the normal regulation of cellular processes and ultimately lead to cancer have been the subject of intense research activity for many decades. These factors can broadly be categorised into two groups (see **Figure 4**):

- ‘endogenous’ factors arising from processes within the body, such as inherited genetic mutations, or hormonal or metabolic factors.
- ‘exogenous’ factors derived from the environment.

Figure 4: Diet, nutrition and physical activity, other environmental exposures and host factors interact to affect the cancer process



The process by which normal cells transform into invasive cancer cells and progress to clinically significant disease typically spans many years. The cancer process is the result of a complex interaction involving diet, nutrition and physical activity, and other lifestyle and environmental factors, with host factors that are related both to inheritance and to prior experience, possibly through epigenetic change. Such host factors influence susceptibility to cancer development, in particular related to the passage of time. This allows both opportunity to accumulate genetic damage, as well as impairment of function, for example, DNA repair processes with ageing. The interaction between the host metabolic state and dietary, nutritional, physical activity and other environmental exposures over the whole life course is critical to protection from or susceptibility to cancer development.

1.3.1 Endogenous factors

1.3.1.1 Inherited mutations

Only a small proportion of cancers (<10 per cent) are linked to specific mutations inherited from an individual's parents (germ-line mutations) [5] and therefore present in every cell in the body that has a nucleus. The inheritance of a cancer-linked germ-line mutation does not mean that a person will ultimately go on to develop cancer, but it does bring with it a higher risk of developing cancer compared with the general population.

Examples of inherited mutations that are linked to cancer are described below:

- Inherited mutations in tumour suppressor genes often increase the chance of developing cancer at a younger age, as with retinoblastoma (a rare cancer of the eye), Li-Fraumeni syndrome, multiple endocrine neoplasia type 1 and kidney cancer in Von Hippel-Lindau disease
- Inherited mutations in the BRCA1 and BRCA2 (breast cancer susceptibility) genes, which are also tumour suppressor genes, lead to defects in DNA repair and cause 5 to 10 per cent of all breast cancer cases.
- People with the syndrome familial adenomatous polyposis (FAP) have a predisposition to colorectal cancer due to mutations in the *adenomatosis polyposis coli* (APC) tumour suppressor gene.

Although these cancer-causing mutations are rare at the population level, inheriting such mutations substantially increases a person's risk of developing these cancers.

As well as kidney, breast and colorectal cancer, other common cancers, including those of the ovary, prostate, pancreas and endometrium, may also be related to inherited mutations, but only in a small percentage of cases.

Even in the absence of single inherited mutations that are known to substantially increase cancer risk, the incidence of some cancers is higher in close family members (for example, colorectal cancer) than in unrelated people. Likely there are several genes that individually affect cancer risk, and in combination can influence cancer risk substantially, that have not been identified.

In people with an inherited genetic predisposition to cancer, the impact of some of the other risk factors for cancer is at least as great as in people without such an inherited susceptibility. In a study among people with Lynch syndrome, the risk of developing colorectal adenomas (a potential precursor lesion for colorectal cancer) was strongly associated with smoking and body mass index [6], much more so than in the general population, suggesting the potential for prevention even in a population of people who are genetically predisposed to colorectal cancer. Insufficient physical activity has also been shown to increase the risk of breast cancer among carriers of BRCA1/2 mutations [7].

1.3.1.2 Steroid hormones

Hormones are a class of signalling molecules produced by specific tissues in one part of the body and transported by the circulatory system to other parts of the body where they have an effect. They help to coordinate tissue and organ functions, playing pivotal roles in the regulation of physiological function, including appetite, metabolism, growth, reproduction and digestion. In humans, hormones can be peptides (small chains of amino acids), proteins or steroids.

Experimental and human studies have demonstrated that imbalances in the homeostasis of various hormone pathways are linked to cancer development and progression.

For example, sex hormones are steroid hormones produced by the gonads (ovaries and testes), adrenal gland or peripheral adipose tissue; they interact with androgen or oestrogen receptors on certain cells and play major roles in human development and function.

Oestradiol, the primary oestrogenic hormone, is a steroid that plays a major role in sexual development and reproduction. It is also known to have significant biological effects on bone, liver and brain tissue.

Prior to menopause, oestradiol is the major oestrogen secreted by the ovaries. In postmenopausal women, after ovarian oestrogen production has ceased, peripheral tissues, such as adipose tissue, and the liver and kidneys, which express aromatase (an enzyme that converts androgens into oestrogens) become the major source of oestrogen. Consequently, greater adiposity is characterised by higher concentrations of circulating oestrogen in postmenopausal women and in men.

Oestrogens stimulate the proliferation of both normal breast tissue and neoplastic breast epithelial cells directly and can promote the development of breast cancer [8, 9]. Higher circulating levels of oestrogens over time are consistently associated with increased risk of breast and endometrial cancers [10, 11].

Exposure to exogenous hormones has also been linked to various malignancies. For example, use of menopausal hormone therapy raises the risk of breast and ovarian cancer, while oral contraceptive use confers a reduced risk of ovarian cancer [12, 13].

1.3.1.3 Insulin and insulin-like growth factor systems

Another hormone system that has been implicated in cancer development is the insulin and insulin-like growth factor (IGF) signalling pathway.

In addition to its metabolic effects in regulating glucose uptake, insulin has mitogenic and anti-apoptotic activity and appears to play a significant role in normal organogenesis. Insulin has been shown to stimulate cell proliferation in normal tissues such as breast tissue and in human cancer cell lines [14]. Administration of exogenous insulin promotes tumour growth in animal models [15].

While the metabolic effects of insulin, such as on glucose transport, are mediated primarily by the phosphatidylinositol 3-kinase (PI3K) pathway, the mitogenic effects of insulin involve the activation of both the PI3K and the mitogen-activated protein kinase (MAPK) pathway.

The IGF system involves two molecules called IGF-I and IGF-II, which bind to specific receptors on cells, as well as at least seven binding proteins (IGFBPs), which regulate the bioavailability and activity of IGF-I and IGF-II. IGF-I and IGF-II are growth factors that share significant structural similarities with insulin, but have much stronger mitogenic and anti-apoptotic effects.

IGF-I and IGF-II both bind to the IGF-I receptor (IGF-IR) and, like insulin, can activate the PI3K and MAPK pathways leading to cell proliferation. IGF-I is the main effector for growth hormone activity and is known to play a role in the survival of transformed cells [16]. IGF-I can also increase levels of vascular endothelial growth factor (VEGF), supporting tumour growth by promoting the growth of new blood vessels [17].



The IGFs differ from most other peptide hormones, such as insulin and growth hormone, in that they are maintained at continuously high levels throughout much of the body. However, their bioactivity is regulated by binding to the IGF-BPs. In fact, 99 per cent of circulating IGF-I is associated with the IGF-BPs, with about 75 per cent specifically bound to IGF-BP-3.

In addition to their IGF-binding properties, certain IGF-BPs (including IGF-BP-3) exhibit direct anti-proliferative and pro-apoptotic effects [18, 19].

A substantial body of epidemiological evidence has now accumulated on the association of circulating IGF-I levels with cancer development. Several meta-analyses and pooled studies have demonstrated robust associations between systemic IGF-I concentrations and breast, prostate and colorectal cancer. Milk consumption is associated with increased circulating IGF-I [20], while calorie-restricted diets, protein restricted diets and fasting regimens are associated with decreased circulating IGF-I in multiple species, including humans [21].

1.3.1.4 Inflammation

Tumour-promoting inflammation is one of the two key enabling characteristics that underlie the hallmarks of cancer (see **Section 1.2.3**) [22, 23].

Inflammation is a normal physiological response to tissue injury. While acute inflammation protects against infectious pathogens, chronic inflammation is associated with DNA and tissue damage, including genetic and epigenetic changes that lead to cancer. Predisposition to chronic inflammation can be acquired through single-gene inheritance (for example, haemochromatosis) and complex multiple-gene inheritance (for example, inflammatory bowel disease).

Inflammation can mediate the association between specific cancer-causing exposures and cancer. Examples of the importance of inflammation follow:

- As well as causing DNA damage, tobacco smoke can induce an inflammatory response that may facilitate lung carcinogenesis.
- The inflammatory response to gastric acid reflux may be responsible for the increased incidence of oesophageal adenocarcinoma.
- Obesity, in particular, has been recognised as a chronic inflammatory condition predisposing both to cardiovascular disease and to cancer. The cellular and molecular basis of this predisposition involves the accumulation of macrophages in the adipose tissue, with the establishment of pro-inflammatory feedback loops (among macrophages, pre-adipocytes and adipocytes) that generate inflammatory cytokines and free radicals.
- The prevention of colon polyps and cancer by aspirin and other anti-inflammatory agents supports a causal link between inflammation and cancer in humans.

Specific inflammatory markers have been linked to cancer development in prospective cohort studies. For example, higher levels of C-reactive protein (CRP), a non-specific marker of an activated inflammatory response, are associated with an increased risk of several cancers, such as lung, colorectal and breast cancer [24, 25].

1.3.1.5 Oxidative stress

Reactive oxygen species generated by normal oxidative metabolism have the potential to cause extensive damage to a cell's macromolecules, such as proteins, DNA and membrane lipids [26]. Several cellular mechanisms are designed to scavenge reactive oxygen species and so prevent this damage. In addition, there are several

endogenous mechanisms for repairing the damage caused by reactive oxygen species and free radicals.

During DNA repair, the damaged oxidised bases can be released and excreted in the urine. One such base, urinary 8-hydroxy-2'-deoxyguanosine, has been used as a surrogate indicator of levels of oxidative DNA damage in humans and rodents.

Several nutrients and non-nutrient phytochemicals have the capacity to quench reactive oxygen species and other free radicals. For example, vitamins C and E can act as antioxidants by donating electrons to free radicals, which can block the damage that free radicals cause. Several other plant-derived compounds (phytochemicals) display antioxidant activity in laboratory experiments. The degree to which these components affect any of the damage caused by free radicals that is related to human cancer remains uncertain.

Obesity may also contribute to oxidative stress and represents one putative mechanism by which excess weight may promote cancer in multiple organs [27, 28]. In addition, weight loss has been shown to reduce various indirect markers of oxidative stress [29].

There is a need to validate improved biomarkers of oxidative stress and the processes that counteract such states, and apply these to rodent and human studies.

1.3.2 Exogenous factors

1.3.2.1 Tobacco

Tobacco use – smoking cigarettes, cigars or pipes, or chewing tobacco – is believed to cause an estimated 20 per cent of all cancer deaths. It is an established risk factor for a number of different cancers, including those of the lung, bladder, liver, pancreas, larynx and colorectum. Tobacco smoke comprises more than 7,000 chemical compounds, including numerous known carcinogens.

The biological mechanisms by which tobacco-derived compounds induce carcinogenesis are well described. For example, following metabolic activation, the activated derivative of benzo(a)pyrene, benzo(a)pyrene diol epoxide, can form DNA adducts in lung epithelial cells [30], thereby causing DNA damage and raising the likelihood of mutation.

Exposure to cigarette smoke may also deplete the body's reserves of nutrients and other components that protect the host from reactive oxygen and free radicals. For example, compared with non-smokers, active smokers have lower circulating concentrations of antioxidant micronutrients – including alpha-carotene, beta-carotene, cryptoxanthin and ascorbic acid – though this may partly be explained by lower intakes of these nutrients among smokers.

It is also clear that quitting smoking has an immediate impact and reduces the risk of lung cancer over time; thus, smoke contains components that promote cancer progression in addition to impacting cancer initiation via DNA damage.

How diet and nutrition impact these processes is not yet clarified.

1.3.2.2 Alcohol

There is strong evidence from the CUP that drinking alcohol is a cause of several cancers (see [Exposures: Alcoholic drinks and Recommendations and public health and policy implications](#)). Other epidemiological analyses have observed a statistically significant decreased risk or no association for Hodgkin lymphoma, non-Hodgkin lymphoma and renal cell carcinoma.

Alcoholic drinks contain several carcinogenic compounds, such as ethanol, acetaldehyde and ethyl carbamate. All of these compounds may contribute to the increased risk of cancer due to alcohol consumption reported in

observational studies. Acetaldehyde, the first metabolite of ethanol to be formed by the metabolic activity of human cells, as well as by that of the microbiota, has been classified as a group 1 carcinogen by the International Agency for Research on Cancer.

The biological mechanisms by which alcohol consumption increases the risk of cancer are likely to include a genotoxic effect of acetaldehyde, alterations in endocrine and growth factor networks, a role as a solvent for tobacco carcinogens, changes in folate metabolism and an impact on DNA repair.

1.3.2.3 Infectious agents

Approximately two million cases of cancer per year, equating to about 15 per cent of the global cancer burden, are attributable to infections. This burden disproportionately affects low- and middle-income countries, where infection rates are higher than in higher-income countries. A number of infectious agents – including viruses, bacteria and parasites – can cause cancer or increase the risk of cancer development.

Some viruses can disrupt normal cell signalling, thereby causing dysregulation of cell growth and proliferation. Many infectious agents are known to cause chronic inflammation, which itself can lead to cancer development – these include viruses such as hepatitis B and C, which are major causes of liver cancer, bacteria such as *Helicobacter pylori*, which is an established cause of stomach cancer, and some parasites.

Both DNA and RNA viruses can cause cancer [31] – DNA viruses can encode viral proteins that inhibit expression of tumour suppressor genes, whereas RNA viruses or retroviruses can encode oncogenes that promote tumorigenesis.

Human papilloma virus (HPV) is an established cause of cervical cancer as well as cancer of the oropharynx, and Epstein-Barr virus is a cause of nasopharyngeal cancer and lymphoma.

Chronic infection with the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis*, which is often associated with consumption of raw or undercooked contaminated freshwater fish, is associated with cholangiocarcinoma (cancer of the bile ducts), and *Schistosoma haematobium* infection is a cause of bladder cancer.

In most cases, infection with one of these agents in itself does not lead to cancer, but is a contributory or necessary factor in the cancer process. Inadequate nutrition or dietary imbalances can lead to immunodeficiencies and increased susceptibility to infections. Dietary factors may also influence host susceptibility to viral infections or persistence of infections.

1.3.2.4 Solar and other radiation

Radiation of certain wavelengths, called ionising radiation, is of sufficient energy to damage DNA and cause cancer. Ionising radiation includes some forms of ultraviolet (UV) light, along with X-rays and gamma rays.

UV light from sunlight can cause some forms of cancer, most notably malignant melanoma of the skin and non-melanoma skin cancer. UV light can be categorised into three bands of varying wavelengths: UVA, UVB and UVC. UVB has the highest energy and is absorbed by the bases in DNA, causing characteristic patterns of DNA damage. UVA damages DNA through the generation of reactive oxygen species.

Other forms of ionising radiation come from cosmic radiation, natural radioactivity present in rocks and soil (such as radon), medical exposure through X-rays, and atomic radiation from weapons and nuclear accidents.

Ionising radiation increases the risk of various cancers, in particular leukaemias and breast and thyroid cancers. Ionising radiation can cause DNA damage, both directly by causing breaks in DNA strands and indirectly by interacting with water molecules and generating reactive oxygen species that damage DNA.

Lower-energy, non-ionising forms of radiation – such as visible light and the energy from cell phones and electromagnetic fields – do not damage DNA and have not been found to cause cancer.

2. Influence of nutrition, body fatness and physical activity on the cancer process

Knowledge that environmental factors in general, and diet, nutrition and physical activity in particular, are critical determinants of the risk of many cancers comes from several different types of evidence.

Patterns of cancer prevalence vary around the world. The prevalence of cancers related to some infections is clearly higher where those infections are most common. High rates of stomach cancer and liver cancer, for example, reflect the occurrence of *H. pylori* and hepatitis viruses respectively.

Other cancers that vary in incidence with geography include breast and colorectal cancers, which are much more prevalent in higher-income countries. Strikingly, though, these geographical patterns in incidence are not fixed. Trends in the incidence of breast and colorectal cancer tend to track with the economic development and industrialisation of countries. Patterns within a single country can show rapid changes over time: for instance, in Japan, breast and colorectal cancers were rare until the 1970s but have risen four- to tenfold

over subsequent decades. Furthermore, in migrant populations, incidence patterns can change to resemble those of the host population within two generations.

This dramatic plasticity in the patterns of incidence of cancer is a persuasive demonstration of the importance of environmental factors in determining cancer development.

Evidence that such environmental determinants of cancer risk include nutrition and physical activity comes from both epidemiological studies (as summarised in the [Exposure sections](#) of the Third Expert Report) and the demonstration of plausible biological mechanisms (as also summarised in [Section 2.2.2](#)).

Foods, drinks, body fatness and physical activity may influence cancer risk in different ways. Foods and drinks may be vectors for specific substances that act as carcinogens through specific pathways. On the other hand, obesity or sedentary ways of life may not act through single discrete pathways, but rather alter the systemic environment to engender a cellular microenvironment that is conducive to cancer development, which may therefore occur at a number of sites (see also mechanisms in [Exposures: Body fatness and weight gain](#), Appendix 2, and [Exposures: Physical activity](#), Appendix 2).

This section outlines specific and general mechanisms by which foods and nutritional factors can, either directly or by creating a cancer-conducive environment, increase the risk of cancer via effects on the processes that lead to the phenotypic characteristics known as the ‘hallmarks of cancer’ (see [Section 1.2.3](#)).

2.1 Influence of nutrition and physical activity on cell regulation

2.1.1 Nutrition, cell differentiation and cancer stem cells

Normal cells become specialised to perform their particular function through a process known as differentiation. Hundreds of different cell types arise from one fertilised egg during development; this is achieved by proliferation and differentiation of a group of cells called stem cells. Stem cells are unspecialised but can give rise to different specialised cell types and thus are key to normal tissue renewal and integrity.

Human tumours may contain a small population of cancer cells known as cancer stem cells, which have both the properties of stem cells and the characteristics of transformed cells. This small population of cells may be important for the development and metastatic spread of these cancers.

In vitro studies and a limited number of animal studies suggest exposure to some bioactive food constituents, including sulphuraphane (organosulphur compound in the isothiocyanate family) and withaferin A (a plant steroidal lactone), can have a profound effect on the differentiation and survival of these cells [32, 33]. Long-chain *n*-3 polyunsaturated fatty acids (PUFAs) in fish oils have been shown to promote differentiation of colonic epithelial cells [34] (see also mechanisms in [Exposures: Meat, fish and dairy products](#), Appendix 2).

In the cancer process, one characteristic of cells that are accumulating DNA damage is that they become de-differentiated in a process called the epithelial-mesenchymal transition (EMT), characterised by loss of cell adhesion and increased cell mobility. Nutritional factors that promote cancer, such as obesity, have been shown to drive EMT in preclinical models [35, 36].

2.1.2 Nutrition and DNA repair

DNA repair is a vital defence in maintaining cellular integrity and preventing cancerous transformation. Various lines of evidence suggest that nutritional factors may influence mechanisms involved in DNA repair.

Data from observational studies have shown that severe malnutrition can impair DNA repair. Repair of nucleotide excisions from DNA has been found to be lower in adults with the lowest intakes of folate.

A number of studies have yielded intriguing findings on the effects of different dietary factors and nutrients on DNA repair capacity. For example, selenium induces repair of nucleotide excisions repair via activation of p53 in cultured fibroblasts [37].

Some dietary components can modify DNA damage and gene expression in exfoliated colonocytes. For example, the amount of single-strand breaks in the DNA of exfoliated colorectal mucosal cells was significantly lower in healthy people consuming a vegetarian diet rich in cruciferous vegetables, yoghurt and chlorophyllin than in people consuming a diet high in meat [38].

Nevertheless, there is a relative paucity of robust data linking nutritional factors to DNA repair capacity and this is an area of future research.

2.1.3 Diet and carcinogen metabolism

The environment contains a multitude of chemicals, both natural and anthropogenic, that have the potential to cause DNA damage, disrupt normal cell function and contribute to carcinogenesis. While humans have been exposed to many of these potential carcinogens for the whole of our evolutionary experience, we have become exposed to some others, such as industrial pollution and cigarette smoke, more recently. Humans have

evolved various physiological mechanisms for protecting against adverse effects of some carcinogens, but these mechanisms may be overwhelmed by large exposures and may not work as well to protect against exposure to unaccustomed types of carcinogens.

Carcinogenesis through exposure to external carcinogens (as opposed to through an imbalance between endogenous causes and protective systems) is the most studied model of cancer. The molecular processes underlying metabolism of carcinogens have been studied intensely. However, much remains to be discovered regarding how these processes function in humans.

One of the major mechanisms by which dietary compounds could influence carcinogenesis is modulation of the pathways by which carcinogens are metabolised.

For a compound to have carcinogenic potential, it generally must undergo metabolic activation to produce reactive intermediates that bind to and damage DNA. A family of enzymes termed phase I and phase II metabolising enzymes, expressed in the liver and in other tissues, are involved in this process.

Metabolic activation of carcinogens is generally catalysed by the cytochrome P450 (CYP) family of phase I enzymes through oxidative reactions. Some of the intermediates formed during this process may be carcinogenic and can bind to DNA, forming DNA adducts. These adducts distort the structure of DNA and disrupt its replication, increasing the likelihood of errors in DNA replication and subsequent mutations.

In addition to P450 phase I enzymes, other systems such as peroxidases (including the cyclooxygenases) and certain transferases, such as N-acetyltransferase and sulphotransferase, can influence carcinogen bioactivation.

Following phase I metabolism, a second group of enzymes, the phase II enzymes, generally 'quench' and neutralise the reactive species generated by phase I metabolism, producing molecules that tend to be more water soluble and can be excreted in bile or urine [39]. Examples include acetyltransferases, glutathione S-transferases (GSTs), UDP-glucuronyltransferases, NAD(P)H:quinone oxidoreductase and sulphotransferases.

The balance of phase I 'activation' and phase II 'detoxification' is important in determining the overall likelihood of carcinogenesis and is a potential target for dietary components that affect cancer risk.

The carcinogenic properties of polycyclic hydrocarbons (produced when meats are cooked at high temperatures), aromatic amines, N-nitroso compounds (found in processed meat) and aflatoxins (produced by certain moulds growing on agricultural crops) result from the metabolism of these compounds, which produces carcinogenic by-products (see also mechanisms in [Exposures: Wholegrains, vegetables and fruit](#), Appendix 2, [Exposures: Meat, fish and dairy products](#), Appendix 2 and [Exposures: Preservation and processing of foods](#), Appendix 2).

The activity of phase I and II metabolising enzymes can be modulated by dietary factors. Some dietary exposures such as isothiocyanates from broccoli and ethanol from alcoholic drinks can induce expression of phase I and II detoxification enzymes (see also mechanisms in [Exposures: Alcoholic drinks](#), Appendix 2). Other dietary constituents that modify carcinogenesis by impacting the host



enzyme systems that activate or inactivate environmental carcinogens include selenium, allyl sulphur, sulphuraphane and isoflavonoids.

In addition to nutrients and non-nutrient phytochemicals inducing the expression of genes involved in carcinogen metabolism, there are many polymorphisms in the genes involved in carcinogen metabolism. Future studies should focus on the complex interactions that influence exposure to specific carcinogens and the possible influence of diet, nutrition and physical activity.

2.1.4 Nutrition and epigenetics

Unlike genetic alterations (which affect the sequence of nucleotides in DNA), epigenetic alterations (which affect the structure of DNA in other ways) can be reversible and are known to be influenced by environmental factors, including diet. For example, dietary folate and other methyl-donors such as choline, methionine and betaine are essential for DNA synthesis and for epigenetic regulation of DNA. Regulated gene expression is maintained by appropriate patterns of DNA methylation, and folate is an important determinant of normal methylation.

Folate deficiency has been shown to result in both hypo- and hypermethylation of specific genes. In animal models, folate deficiency results in hypomethylation of the TP53 gene as well as increased DNA methyltransferase activity, though with continued folate deficiency, an increase in both TP53 and genome-wide methylation is observed. In addition, dietary constituents such as genistein, which do not provide methyl groups, have also been reported to modify DNA methylation.

Imbalances in, or lack of, specific dietary constituents may potentially increase the risk of cancer by inducing an imbalance in DNA precursors, leading to altered DNA synthesis, repair and methylation patterns, with

consequences for gene expression.

Folate deficiency has been linked to the inappropriate inclusion of uracil (a base not usually part of the DNA sequence) in DNA, which leads to genomic instability and a failure of DNA repair [40].

2.2 Impact of diet, nutrition and physical activity on the cancer process

Maintenance of the normal structure and function of cells, tissues and the whole body is a prerequisite for health. The development of cancer represents a failure to sustain this maintenance. Cancer develops when the normal regulation of cells is disrupted by stress from endogenous or external challenges. It happens when there is an imbalance between the factors that predispose to cancer and the capacity of the system to withstand them.

The foods and drinks consumed in a diet comprise a complex set of exposures, which not only provides the ultimate source of energy and nutrients for normal growth, development and maintenance of function, but may also act as the vehicle for other substances that have potentially beneficial, neutral or adverse effects. Information on the specific links between patterns of diet, consumption of specific foods and physical activity on the one hand, and the risk of the development of cancers on the other, comes from a combination of different types of evidence, including the findings of epidemiological research, and of clinical, *in vivo* and *in vitro*, laboratory studies (in both humans and animals).

Some links between diet or physical activity and cancer are specific, such as the relationship between consumption of red and processed meat and colorectal cancer, and site-specific mechanisms can be identified to account for them (see mechanisms in

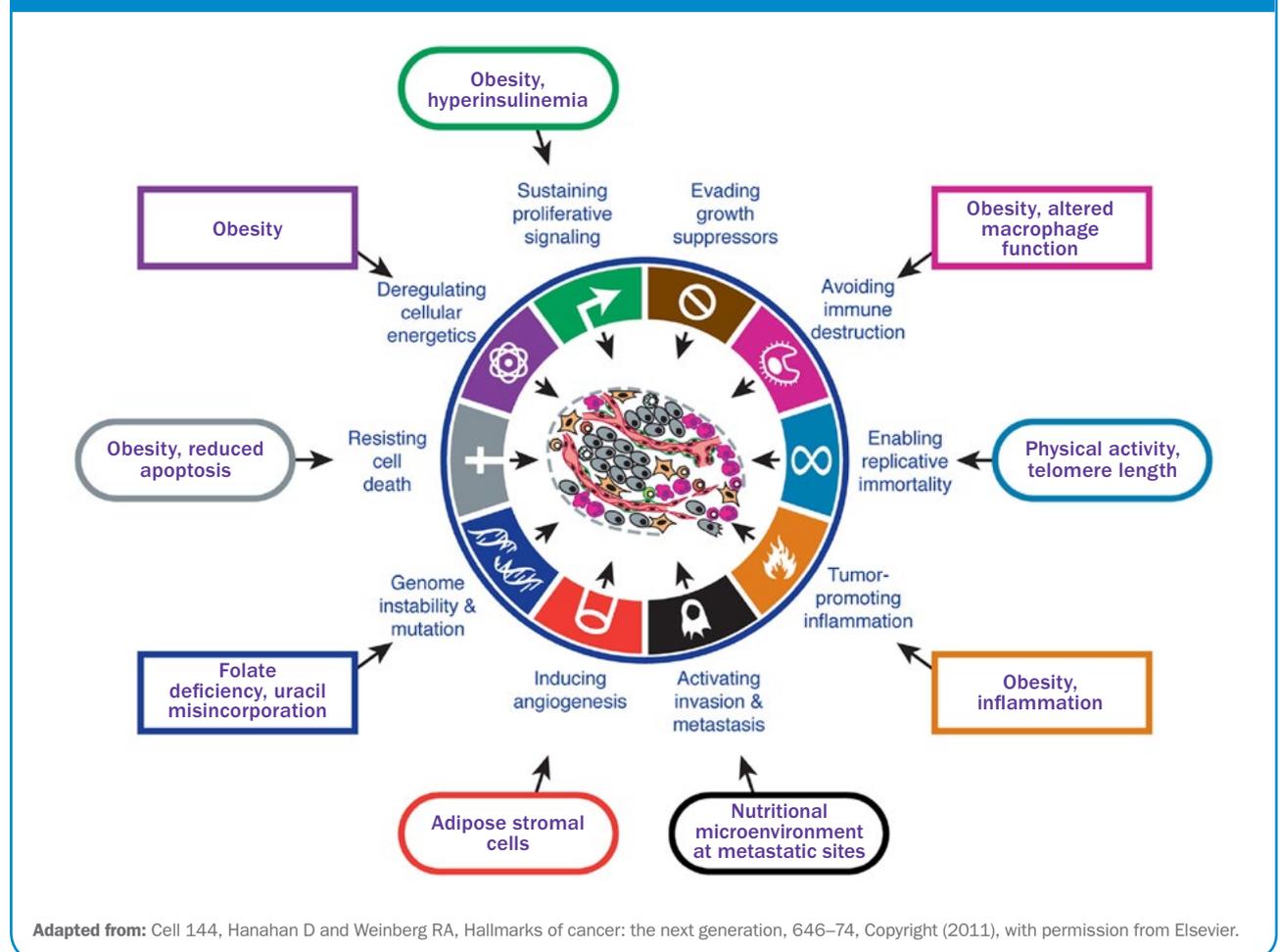
Exposures: Meat, fish and dairy products, Appendix 2, and Exposures: Preservation and processing of foods, Appendix 2). On the other hand, several exposures relating to nutrition and physical activity are linked to more than one, sometimes several, different cancer types. An example is excess body fatness. These exposures might operate through different mechanisms for each cancer site, but more likely are responsible for creating a broader systemic environment conducive to cancer development across several tissues (see mechanisms in Exposures: Body fatness and weight gain, Appendix 2).

A growing body of evidence is making it increasingly possible to identify possible relationships between the effects of nutritional factors and physical activity measured at the

level of the whole body in epidemiological or clinical human studies and disrupted molecular pathways, and ultimately with the phenotypic changes in structure and function that are characterised as the hallmarks of cancer (see **Figure 5**). Each of these hallmarks, or capabilities, represents an essential part of the biology of a cancer cell, and nutritional factors can have an impact on each of them. Nutrition is, therefore, a critical determinant of the potential of a healthy cell to acquire the characteristics of a cancer cell.

The combined evidence on fundamental biology and epidemiology provides a compelling case for a causal connection between diet, nutrition and physical activity, and the risk of several cancers.

Figure 5: Nutrition, physical activity and the hallmarks of cancer



A wide range of factors related to diet, nutrition and physical activity can influence the processes represented by the hallmarks of cancer.

2.2.1 Impact of nutrition and physical activity on the hallmarks of cancer – using body fatness as an example

This section demonstrates how nutritional factors or physical activity levels can influence cancer development and progression by impacting some of the hallmarks of cancer, using body fatness as an example (see **Figure 6**). The mechanisms by which body fatness has an impact on cancer development are likely numerous, but emerging evidence from both experimental models and human studies indicates that increased body fatness engenders a metabolic state that is conducive to accumulating the genetic and epigenetic alterations that lead to cancer.

See also mechanisms in [Exposures: Body fatness and weight gain](#), Appendix 2.

2.2.1.1 Sustained proliferative signalling

Unlike most healthy cells, cancer cells do not typically require stimulation from growth factors or other signals to proliferate. Cancer cells may acquire this ability in a number of ways:

- Many cancer cells produce growth-promoting signals themselves.
- Cancer cells can also permanently activate the growth and survival pathways that normally respond to growth factors, via mutations that lock-in these signals. For instance, PI3K mutations activate the PI3 kinase/Akt/mTOR pathway independently of growth factors such as insulin or insulin-like growth factor-1.
- Some cancer cells also deactivate regulatory signals by downregulating 'off switches' that prevent excessive growth. For example, many cancer cells silence PTEN, which downregulates insulin/PI3K once those pathways are activated.

Many of the metabolic and endocrine abnormalities associated with obesity, such as elevated levels of fasting insulin and oestradiol, as well as inflammatory mediators associated with obesity, exert proliferative effects. Therefore, in the obese state, there is a general upregulation of cell growth.

2.2.1.2 Resisting cell death

Normal cells have the ability to 'self-destruct' under certain conditions, a process known as apoptosis. This happens, for example, when a cell's DNA is damaged beyond repair.

In contrast, cancer cells can downregulate apoptosis and survive, even following severe DNA damage. They may do this by altering the mechanisms that detect DNA damage or abnormalities.

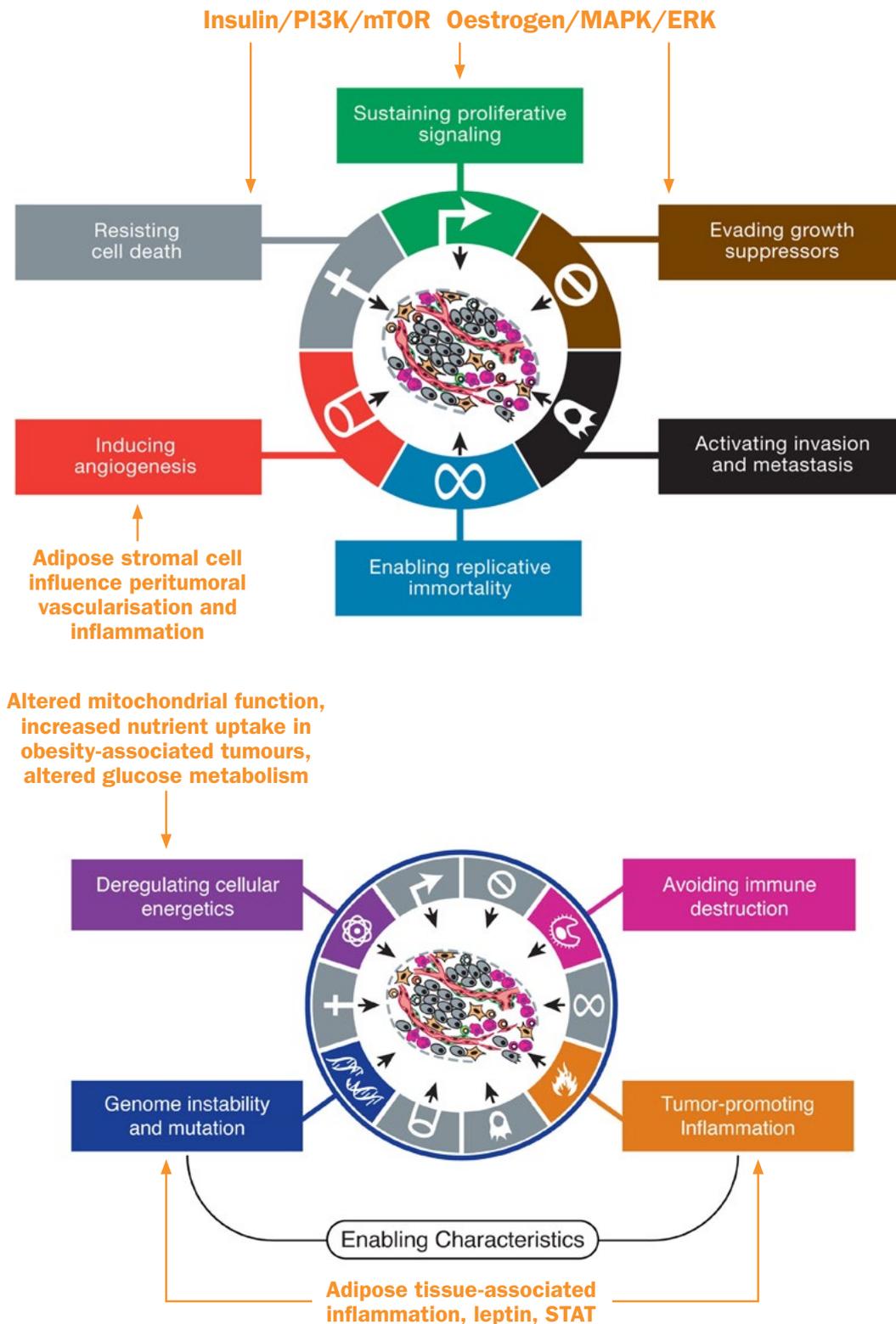
Insulin, oestradiol and inflammatory pathways, which are all up-regulated in obesity, are known to exhibit anti-apoptotic properties. Therefore, in obesity there is a general suppression of cell death – a hallmark of the cancer process.

2.2.1.3 Activating invasion and metastasis

Cancer cells can infiltrate the local tumour microenvironment (invasion) and spread to distant organs via the bloodstream or lymphatic system (metastasis). While traditionally considered as a late event in the clinical course of cancer, metastasis can actually occur at any stage of tumorigenesis.

Tumour cells untether themselves from the extracellular matrix by expressing proteins that degrade it, notably matrix metalloproteases. The cells often undergo a process termed epithelial-to-mesenchymal transition, characterised by a decrease in expression of epithelial markers such as E-cadherin, and an increase in expression of mesenchymal markers such as N-cadherin, so they become less physically connected

Figure 6: Obesity and the hallmarks of cancer



Adapted from: Cell 144, Hanahan D and Weinberg RA, Hallmarks of cancer: the next generation, 646–74, Copyright (2011), with permission from Elsevier.

Several of the cancer hallmarks, and both enabling characteristics, can be affected by factors relating to diet, nutrition and physical activity. Obesity illustrates the wide range of cellular and molecular processes that may be affected to promote cancer development and progression.

Abbreviations: ERK, extracellular signal-regulated kinases; MAPK, mitogen-activated protein kinase; mTOR, mechanistic/mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription.

to their neighbouring cells and extravasate through blood vessels to distant sites.

Metastatic cancer cells also display other features of aggressive cancer, such as increased motility and apoptotic resistance, further facilitating travel to and survival in distance sites.

Certain tissues are particularly prone to acting as colonisation sites for metastatic tissue, such as the liver, bones, brain and lung. This suggests that the specific microenvironment in these tissues is more favourable for the support of tumours than that of other tissues. Nutritional factors and body fatness are an important determinant of the tissue microenvironment.

Most tumours are also enriched to varying degrees with cancer stem cells, which share several characteristics with tissue stem cells as well as metastatic cells.

2.2.1.4 Inducing angiogenesis

Angiogenesis is the term for the growth and establishment of a vascular network. As a tumour develops, relying on the local vascular supply alone causes local hypoxia, which activates genes that lead to the expression of growth factors, such as vascular endothelial growth factor (VEGF). These stimulate the migration and replication of endothelial cells and their differentiation into cancer-associated vascular networks, which are needed to support local tumour growth. Normal cells, by contrast, do not retain the capacity to promote angiogenesis. In addition, enhanced angiogenesis is important for metastatic cells to support growth at distant sites.

Adipose stromal cells may also influence tumour vascularisation. Tumour vascularisation is increased in obese mice, with associated increases in the proliferative activity of perivascular tumour cells and periadipocyte tumour cells.

2.2.1.5 Genome instability and mutation

Genomic instability is an increased tendency of the genome to acquire mutations because of dysfunction in the process of maintaining the genome. It can be thought of as an underlying enabling characteristic, which expedites cells' acquisition of the other hallmarks of cancer.

Genomic instability can be classified into two pathways: the microsatellite instability (MIN) and chromosomal instability (CIN) pathways. Screening for the levels of MIN in tissues reveals whether tissues have a microsatellite-stable (MSS) or microsatellite-unstable (MSI) profile.

Human studies have shown that obesity is associated with an increased risk of microsatellite high (MSI-H) colorectal and endometrial cancer in women [41, 42], linking genomic instability with the obese



phenotype. Visceral obesity is associated with genomic instability events, such as induction of anaphase bridges and altered expression of spindle assembly checkpoint genes, both *in vitro* and *in vivo* in oesophageal adenocarcinoma [36].

2.2.1.6 Tumour-promoting inflammation

Tumour-promoting inflammation can also be thought of as an underlying enabling characteristic, which can inadvertently contribute to cells' acquisition of multiple other hallmark capabilities.

Chronic inflammation has long been recognised as a feature of cancer. Several inflammatory conditions are established precursors for specific cancers, including gastritis for gastric cancer, inflammatory bowel disease for colon cancer and pancreatitis for pancreatic cancer.

Chronic inflammation has been implicated in the link between nutrition and cancer in a large number of epidemiological and preclinical studies. In particular, obesity is now recognised as a chronic inflammatory state that predisposes to cancer. There are complex interactions between the underlying cellular, molecular and metabolic factors involved in the nutrition-inflammation-cancer triad.

Adipose tissue acts as a store of lipid as triglycerides, for use during periods of energy deficit. Engorgement of adipocytes with triglycerides is thought to be the basis for the chronic inflammatory state that accompanies obesity.

Adipose tissue is a metabolically active tissue containing a number of stromal cells – including pre-adipocytes, vascular cells and fibroblasts – and a host of immune cells such as adipose tissue macrophages (ATMs). Adipose tissue secretes leptin, and in obesity adiponectin secretion is reduced, with both of these effects tending to be pro-inflammatory.

Obesity is also associated with elevated secretion of a number of pro-inflammatory cytokines, including interleukin-6, interleukin-8 and tumour necrosis factor- α .

See also mechanisms in Appendix 2 of:

- Exposures: Alcoholic drinks
- Exposures: Body fatness and weight gain
- Exposures: Non-alcoholic drinks
- Exposures: Other dietary exposures
- Exposures: Physical activity

2.2.2 Nutrition, body fatness, height, physical activity and susceptibility to cancer

This section focuses on exposures that contribute to the development of cancer at more than one site, as supported by strong evidence identified in the Third Expert Report. The section describes general mechanisms by which these exposures might influence the systemic and cellular microenvironment in ways that shift normal cell function towards one or more of the specific hallmarks of cancer. These effects are summarised in the table that follows.

2.2.2.1 Body fatness

There is strong evidence from the CUP that greater body fatness is a cause of many cancers (see [Exposures: Body fatness and weight gain](#) and [Recommendations and public health and policy implications](#)). This evidence has strengthened over the last decade.

Multiple cellular and molecular pathways are implicated in the link between greater degrees of adiposity and cancer. Increasing adiposity leads to systemic changes in diverse metabolic and endocrine pathways that can impact upon intracellular pathways relevant to various hallmarks of cancer including sustained proliferative signalling, resisting cell death, invasion and metastasis, angiogenesis, altered cellular energetics, genomic instability, immune regulation and inflammation.

Hormonal profiles, in particular oestrogen, and growth factors such as insulin, are commonly dysregulated in obesity. For example, in postmenopausal women increased aromatase activity in adipose tissue leads to elevated oestrogen levels, which can stimulate proliferation of normal breast tissue and neoplastic breast epithelial cells directly, and can promote the development of ER-positive, oestrogen-dependent breast cancer by both endocrine and paracrine mechanisms [43].

Hyperinsulinemia is also a common phenomenon in obesity. In addition to its metabolic effects, insulin has mitogenic and anti-apoptotic properties. Hyperinsulinemia has been associated with elevated risk of various malignancies including postmenopausal breast, colorectal and endometrial cancers [44–46], and recent findings from large-scale Mendelian randomisation studies suggest a causal link between insulin and both endometrial and pancreatic cancer [47, 48].

Adipose stromal cells may influence tumour vascularisation, which is increased in obese mice, with associated increases in the proliferative activity of tumour cells.

The deregulation of cellular energetics, another hallmark of cancer, is also a common feature of obesity, as evidenced by altered mitochondrial function as well as elevated nutrient uptake in obesity-associated tumours [49, 50].

Obesity is also associated with genomic instability, including both the microsatellite instability pathway (MSI – a marker of defective DNA repair mechanisms) and the chromosomal instability (CSI) pathway. However, data linking obesity to specific tumours defined by MSI status are limited and inconsistent.

Adipose tissue contains a unique repertoire of immune cells. In obesity, there is a substantial increase in the number of macrophages residing in adipose tissue. This infiltration of macrophages into adipose tissue is associated with the secretion of pro-inflammatory cytokines, including interleukin-6 and tumour necrosis factor- α , contributing to both local and systemic inflammation. Circulating pro-inflammatory cytokines and other inflammatory factors have been associated with breast and colorectal cancers in human studies [51, 52].

Inflammation leads to sustained signalling through the STAT3 and NF- κ B signalling pathways and subsequent cell proliferation and enhanced cell survival through anti-apoptotic mechanisms. Inflammation may also have indirect effects on cancer risk, for example, through worsening insulin sensitivity and raising circulating insulin levels.

2.2.2.2 Height

There is strong evidence from the CUP that developmental factors leading to greater growth in length in childhood (marked by adult attained height) is a cause of many cancers (see [Exposures: Height and birthweight and Recommendations and public health and policy implications](#)). The association of height with such a broad range of cancer sites suggests that height is a marker of one or more biological mechanisms that create a structural and functional phenotype of increased susceptibility to cancer in general.

An adult's height reflects a complex interplay of genetic, hormonal, nutritional and other environmental factors that affect growth



within the womb, and during childhood and adolescence. Even exposures that occur before conception may be relevant, including those affecting previous generations.

The trajectory and pattern of growth are also linked to rates and stages of maturation, such as age at menarche, which are themselves related to hormonal exposures linked to cancer risk, such as lifetime exposure to oestrogens.

Height is a marker of all these factors and is unlikely to affect the risk of cancer directly.

One mechanism hypothesised to underlie the association of greater height with increased cancer risk is exposure to growth factors, such as growth hormone and insulin-like growth factors (IGFs), in childhood and early adulthood [53, 54]. Taller people generally have higher circulating levels of IGF-I during adolescence and elevated signalling through the insulin-IGF axis, which lead to activation of the phosphatidyl-3-kinase-mTOR and MAPK pathways, leading to cellular proliferation, suppressed apoptosis and angiogenesis. Further, higher concentrations of circulating IGF-I are associated with greater risk of breast, colorectal and prostate cancer – some of the cancer sites where greater adult height is a risk factor [55, 56]. Mendelian randomisation studies that have assessed the relationship between gene variants linked to greater height and cancer provide additional evidence for a relationship between greater height and risk of breast and colorectal cancers [57, 58].

Other proposed mechanisms include the hypothesis that taller people have more stem cells and thus there is greater opportunity for mutations leading to cancer development [59]. In addition, there may be site-specific mechanisms at play, for example, for colorectal cancer, taller adults have longer intestines with a greater number of cells at risk; therefore, there may be greater potential for exposure to mutagenic or cancer-promoting agents.



2.2.2.3 Physical activity

There is strong evidence from the CUP that physical activity protects against cancers of the colon, breast and endometrium (see [Exposures: Physical activity and Recommendations and public health and policy implications](#)). There is also strong evidence that physical activity helps prevent excess weight gain and obesity (see [Energy balance and body fatness](#)). Therefore, physical activity may also indirectly contribute to a reduced risk of obesity-related cancers, likely through multiple mechanisms such as reductions in circulating oestrogen levels, insulin resistance and inflammation – all of which have been linked to cancer development at various anatomical sites.

Evidence on mechanisms includes the following:

- Physical activity improves insulin sensitivity and reduces fasting insulin levels, which may decrease the risk of breast, colorectal and endometrial cancers [46, 60].
- Exercise may affect breast cancer risk through its effects on insulin-like growth factors (IGFs) [61], because high levels of circulating IGF-I are associated with increased risk of several cancers, including breast, prostate and colorectal cancers [62].
- Physical activity has been shown to have immunomodulatory effects, enhancing innate and acquired immunity, and promoting tumour surveillance [60, 63].

- Studies have shown that aerobic exercise can decrease oxidative stress and enhance DNA repair mechanisms, decreasing carcinogenesis [63].
- Physically active people tend to have higher exposure to sunlight and consequently increased vitamin D, which may modify cell proliferation [64].

2.2.2.4 Red and processed meat

There is strong evidence from the CUP that consumption of red meat and consumption of processed meat are both causes of colorectal cancer (see [Exposures: Meat, fish and dairy products](#) and [Recommendations and public health and policy implications](#)).

Greater consumption of red and processed meat may be a marker for a 'Western type' diet (an aggregation of several related exposures) which could be associated with higher risk of various cancers.

Nevertheless, a number of biological mechanisms are hypothesised to underlie the association of red and processed meat with cancer:

- Cooking meats at high temperatures results in the formation of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), which have mutagenic potential through the formation of DNA adducts and have been linked to cancer development in experimental studies.
- Haem iron, which is present at high levels in red meat, has been shown to promote colorectal tumorigenesis by stimulating the endogenous formation of carcinogenic N-nitroso compounds [65]. Haem iron intake has been associated with an increased risk of colorectal tumours harbouring transitions from guanosine to adenine in *KRAS* and *APC* in a large prospective cohort study, which suggests that alkylating rather than oxidative DNA-damaging mechanisms

are involved in haem-induced colorectal carcinogenesis [66].

- Processed meat tends to be higher in fat than red meat, and this may stimulate tumorigenesis through synthesis of secondary bile acids; however, human data supporting this hypothesis are weak.
- Processed meat is a source of exogenously-derived N-nitroso compounds, which have carcinogenic potential [67].
- High salt content of processed meat may result in damage to the stomach mucosal lining leading to inflammation, atrophy and *H. pylori* colonisation.

2.2.2.5 Vegetables and fruit

There is strong evidence that the risk of aerodigestive cancers is reduced by a diet characterised by higher intakes of a range of non-starchy vegetables and fruit. Although there is limited evidence suggesting that consumption of specific categories of non-starchy vegetables and fruit, and some of their constituents, reduces the risk of a range of specific cancers, the consistency of the findings across a range of related exposures, and several cancers, strengthens the evidence. There is also limited evidence that non-starchy vegetables and fruit protect against weight gain, overweight and obesity (see [Exposures: Wholegrains, vegetables and fruit](#) and [Recommendations and public health and policy implications](#)).



Vegetables and fruit are a diverse and complex food group. They are a rich source of various nutrients that can impact cancer risk, such as vitamins C and E, selenium and folic acid. A substantial body of experimental data links many of these compounds with anti-tumorigenic effects in various cells in both animal and *in vitro* models [68].

Consumption of vegetables and fruit also provides the host with thousands of phytochemicals, which are not nutrients but may have bioactivity in humans. Several phytochemicals have been shown in laboratory studies to have various anti-cancer properties, which might contribute to a protective effect against cancer in humans. These include dietary fibre, carotenoids, dithiolthiones, glucosinolates and indoles, isothiocyanates, flavonoids, phenols, protease inhibitors, plant sterols, allium compounds and limonenes.

However, although there is evidence for plausible mechanisms underpinning an effect of vegetables and fruit in general, or components within them, on reduced risk of cancers in general, there is a lack of robust experimental evidence from carefully controlled human studies for specific mechanisms linking particular foods, or compounds found within them, with individual cancer types.

2.2.2.6 Alcohol

There is strong evidence from the CUP that drinking alcohol is a cause of several cancers (see [Exposures: Alcoholic drinks](#) and [Recommendations and public health and policy implications](#)). The mechanisms by which chronic alcohol consumption leads to cancer development appear to be diverse:

- Acetaldehyde, a toxic metabolite of ethanol oxidation, can be carcinogenic to some cell types, for example, colonocytes [69].
- Higher ethanol consumption can also induce oxidative stress through increased production of reactive oxygen species, which are genotoxic and carcinogenic [70].



- Alcohol may also act as a solvent for cellular penetration of dietary or environmental (such as tobacco) carcinogens, or interfere with retinoid metabolism and DNA repair mechanisms [71].
- Alcohol has been linked to changes in hormone metabolism and, for example, is associated with increased levels of oestradiol [72, 73].
- More recent research has focused on the impact of chronic high alcohol intake on dysbiosis of the gut microbiome and weakened gut barrier function [74]. Higher exposure to bacterial products leaked from the gut lumen has been associated with higher risk of colorectal cancer development [75].

Table 1 summarises the general mechanisms underpinning the biological pathways that link specific exposures to discrete cancer hallmarks. The columns show the physiologic or metabolic impact at the systemic level, and the potential molecular or cellular pathways that are affected, which then lead to one or more of the phenotypic changes that characterise cancer (hallmarks).

Table 1: Potential impact of diet, nutrition, physical activity and height in increasing susceptibility to cancer

| Exposure | Systemic impact | Cell function | Hallmarks possibly affected |
|---|--|--|---|
| Greater body fatness | Hyperinsulinemia | mTOR/PI3K/AKT, MAPK | Reduced apoptosis; increased proliferation; genome instability |
| | Increased oestradiol | MAPK/ERK/PI3K | Increased proliferation in ER-positive tissues; genome instability |
| | Inflammation | STAT3/NF-κB | Reduced apoptosis; increased cell division; altered macrophage function; genome instability |
| | | WNT, P53 | Cellular energetics |
| Greater height | Higher IGF-I | mTOR/PI3K/AKT, MAPK | Reduced apoptosis; increased proliferation |
| Greater physical activity | Reduction in insulin | mTOR/PI3K/AKT, MAPK | Increased apoptosis; reduced proliferation; less genome instability |
| | Reduction in oestradiol and testosterone | MAPK/ERK/PI3K | Reduced proliferation in ER-positive tissues; reduced genome instability |
| | Reduced inflammation (long term); improved immune function | STAT3/NF-κB | Increased apoptosis; increased cell division; altered macrophage function; reduced genome instability |
| | | WNT, P53 | Cellular energetics |
| Greater intake of red and processed meat | Elevated exposure to nitrites; endogenous N-nitroso compound formation | DNA adduct formation -> mutations in p53, KRAS | Reduced apoptosis; increased proliferation; genomic instability |
| | | Oxidative stress, inflammation | Increased inflammation; genomic instability |
| Greater intake of dairy foods | Higher IGF-I | mTOR/PI3K/AKT, MAPK | Reduced apoptosis; increased proliferation |
| Lower vegetables and fruit intake | Folate deficiency | DNA uracil misincorporation | Genome instability |
| | Low dietary fibre intake | Low butyrate | Reduced apoptosis; increased proliferation |
| | Low levels of carotenoids, vitamins A, C, E | Oxidative stress, inflammation | Increased inflammation; genomic instability; reduced apoptosis; increased proliferation |
| Greater alcohol intake | Elevated acetaldehyde | Oxidative stress, lipid peroxidation | Increased inflammation; genomic instability |
| | Increased oestradiol | MAPK/ERK/PI3K | Increased proliferation in ER-positive tissues |
| | Inflammation | STAT3/NF-κB | Reduced apoptosis; increased cell division; altered macrophage function |
| | Folate deficiency; interference with 1-carbon metabolism | DNA uracil misincorporation | Genome instability |

Abbreviations: AKT, also known as protein kinase B; DNA, deoxyribonucleic acid; ER+, oestrogen receptor positive; ERK, extracellular signal-regulated kinases; IGF-I, insulin-like growth factor 1; KRAS, please see glossary; MAPK, mitogen-activated protein kinase; mTOR, mechanistic/mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; P53, tumour protein p53; PI3K, phosphoinositide 3-kinase; STAT3, signal transducer and activator of transcription 3; WNT, Wingless-related integration site.

3. Conclusions

The seeds of cancer lie in the complex genetic features that every cell inherits.

As an organism develops, its cells display a range of functional and structural characteristics that are appropriate to each stage of development. These include behaviours that are typical of cancer cells, including rapid cell division and invasion of surrounding tissue.

If these capabilities are inappropriately activated at other times, because of genetic mutations or faulty epigenetic control of gene expression, then cells may accumulate sufficient abnormalities to behave in the way that defines cancer. These capabilities of cells have been called the hallmarks of cancer.

Cells have evolved a range of mechanisms to prevent the accumulation of such abnormalities:

- Eliminating or detoxifying external agents that can cause DNA damage
- Repairing DNA damage so it is not transmitted to daughter cells
- Ensuring cells with damaged DNA do not survive

However, these protective mechanisms are not perfect and may be compromised by several things:

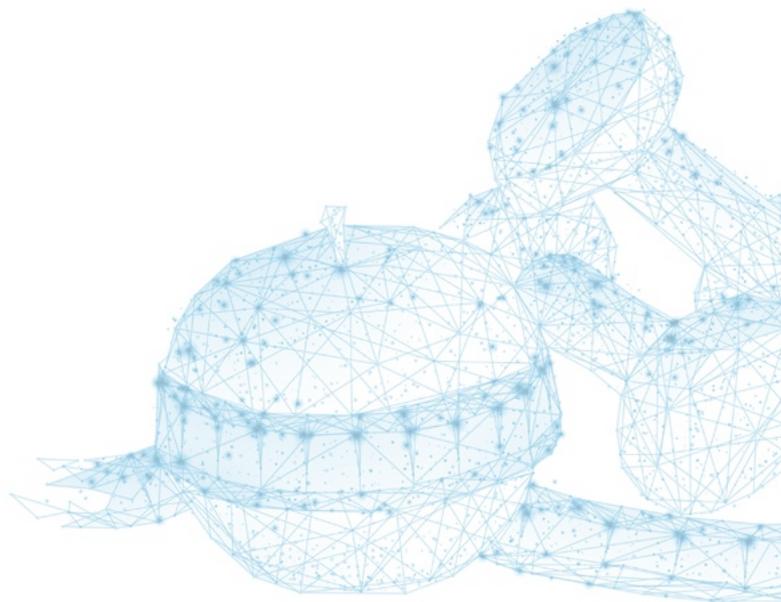
- Inherited genetic defects in the host
- Overwhelming levels of exposure to external carcinogens
- Endogenous factors that compromise DNA integrity
- Reduced effectiveness of endogenous protective systems

In many cases a combination of these factors may operate. Nutritional factors, physical activity and body fatness are important determinants of the function of these protective processes.

Ageing allows increasing opportunity for cells to accumulate the DNA damage that is necessary for a tumour to develop. In addition, ageing is accompanied by a general loss of functional capacity.

Furthermore, effective function depends on the availability of appropriate nutrition, to provide the substrates and cofactors necessary for normal metabolism. Inappropriate nutrition at the whole-body level is reflected in a disordered nutritional microenvironment at the cellular and molecular levels. This creates an environment that is conducive to the accumulation of DNA damage and therefore to cancer development.

Reduced functional capacity, which occurs with ageing and with inappropriate nutrition, reduces the resilience of organisms to endogenous or external stresses.



Hence a constellation of factors relating to ageing and to the external and internal environments determines the likelihood that a particular cell may develop the pattern of abnormal DNA structure and therefore the function that leads to cancer.

Epidemiology has demonstrated beyond doubt that while for any individual, genetic factors may contribute to susceptibility to cancer, at a population level the patterns of cancer are principally determined by modifiable factors. Both epidemiological and experimental evidence suggest that the main modifiable factors are tobacco use, together with nutritional factors (including not only diet, but also body composition, adiposity and energy balance) and physical activity.

Diet, body composition, energy balance and physical activity are essential aspects of human existence. Imbalanced and inappropriate levels of these factors can disturb normal homeostasis and reduce resilience to external challenges. This may manifest in many ways, for instance as susceptibility to infections, to cardiometabolic disease or to cancer.

The precise mechanisms by which individual nutritional exposures, or combinations of them, interact over the whole life course to create a cellular microenvironment conducive to cancer are not yet completely understood. However, there is sufficient and accumulating evidence for a fundamental role of nutrition at the whole-body level in determining patterns of cancer in populations, and cancer risk in individuals, through influencing the cellular microenvironment and the basic molecular functions of cells.



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Abbreviations

| | |
|-------------------------|--|
| AICR | American Institute for Cancer Research |
| AKT | also known as protein kinase B |
| APC | <i>Adenomatous polyposis coli</i> |
| ATMs | Adipose tissue macrophages |
| BRCA | BReast CAncer susceptibility gene |
| CIN | Chromosomal instability |
| CRP | C-reactive protein |
| CUP | Continuous Update Project |
| CYP | Cytochrome P450 |
| DNA | Deoxyribonucleic acid |
| EMT | Epithelial-mesenchymal transition |
| ER+ | Oestrogen receptor positive |
| ERK | Extracellular signal-regulated kinases |
| FAP | Familial adenomatous polyposis |
| GSTs | Glutathione S-transferases |
| GWAS | Genome-wide association studies |
| <i>H. pylori</i> | <i>Helicobacter pylori</i> |
| HAT | Histone acetyltransferase |
| HCAs | Heterocyclic amines |
| HDAC | Histone deacetylase |
| HPV | Human papilloma virus |
| IARC | International Agency for Cancer Research |

| | |
|--------------------------------|--|
| IGF | Insulin-like growth factor |
| IGFBPs | Insulin-like growth factor binding proteins |
| MAPK | Mitogen-activated protein kinase |
| MIN | Microsatellite instability |
| mRNA | Messenger ribonucleic acid |
| MSI | Microsatellite-unstable |
| MSS | Microsatellite-stable |
| mTOR | Mechanistic/mammalian target of rapamycin |
| NCDs | Non-communicable diseases |
| NF-κB | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| P53 | Tumour protein p53 |
| PI3K | Phosphatidylinositol 3-kinase |
| PAHs | Polycyclic aromatic hydrocarbons |
| PTEN | Phosphatase and tensin homolog |
| PUFAs | Polyunsaturated fatty acids |
| RNA | Ribonucleic acid |
| ROS | Reactive oxygen species |
| SNPs | Single nucleotide polymorphisms |
| STAT | Signal transducer and activator of transcription |
| TP53 | Tumour protein p53 |
| UV | Ultraviolet |
| VEGF | Vascular endothelial growth factor |
| WCRF | World Cancer Research Fund |
| WNT | Wingless-related integration site |

Glossary

Acetaldehyde

The major metabolic product of ethanol, which is generated by ethanol dehydrogenase and subsequently metabolised to acetate by aldehyde dehydrogenase.

Acetylation

The introduction of an acetyl group (CH₃CO-) into a compound. Acetylation of histone proteins in chromosomes tends to activate genes or facilitate transcription of genes into mRNA and translation of mRNA into protein.

Acute

Describing a condition or disease that lasts a short time, comes on rapidly, and is often accompanied by distinct symptoms.

Adenine

A purine derivative and one of the four possible nitrogenous bases in nucleotides and nucleic acids (DNA and RNA). Base pairs with thymine.

Adenocarcinoma

Cancer of glandular epithelial cells.

Adenomatous polyposis coli (APC) gene

A gene that provides instructions for making the APC protein, which plays a critical role in several cellular processes. The protein acts as a tumour suppressor, keeping cells from growing and dividing too fast or in an uncontrolled way.

Adipocytes

Cells of adipose tissue, where fats (triglycerides) are stored.

Adipose tissue

Body fat. Tissue comprising mainly cells containing triglyceride (adipocytes). It acts as an energy reserve, provides insulation and protection, and secretes metabolically active hormones.

Adiposity

Degree of body fatness; can be measured indirectly in a variety of ways including body mass index (see **body mass index**) and percentage body fat.

Aerobic physical activity/exercise

Relating to or denoting exercise taken to improve the efficiency of the body's cardiovascular system in absorbing and transporting oxygen.

Aflatoxins

Naturally occurring mycotoxins that are produced by many species of *Aspergillus*, a fungus, most notably *Aspergillus flavus* and *Aspergillus parasiticus*. Aflatoxins are toxic and carcinogenic to animals, including humans.

Alcohol

An organic compound that contains a hydroxyl group bound to a carbon atom. Releases energy when metabolised in the body. Commonly ethanol C₆H₅OH.

Amino acids

Building blocks of proteins that possess both a carboxyl (-COOH) and an amino (-NH₂) group attached to the same carbon atom and are water-soluble organic compounds.

Anaphase bridge

When telomeres of sister chromatids fuse together and fail to completely segregate into their respective daughter cells during mitosis. Most prevalent during the anaphase, when sister chromatids move to opposite ends of the spindle fibre.

Androgen

Any masculinising sex hormone, such as testosterone.

Angiogenesis

The process of generating new blood vessels.

Anthropogenic

Originating in human activity, usually related to environmental pollution and pollution.

Apoptosis

The death of cells that occurs as a normal and controlled part of the cell cycle.

Autocrine

Denoting a mode of hormone action in which a hormone binds to receptors on and affects the functions of the same cell that produced it.

Basal metabolism

The minimum amount of energy required to maintain vital functions at complete rest, measured by the basal metabolic rate in a fasting individual who is awake and resting in a comfortably warm environment.

Bioactivity

The effect of a given agent on a living organism or on living tissue.

Bioavailability

Degree to which a drug or other substance becomes available to the target tissue after administration.

Biological mechanisms

System of causally interacting processes that produce one or more effects.

Biomarker

A naturally occurring molecule, gene or characteristic by which a particular pathological or physiological process can be identified.

Body composition

The composition of the body in terms of the relative proportions of water and adipose and lean tissue. Can also be described as the proportions of fat (lipid) and fat-free mass. May also include the content of micronutrients, such as iron, and the distribution of adipose tissue, for example, central/peripheral or visceral/subcutaneous.

Body mass index (BMI)

Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m²). Provides an indirect measure of body fatness.

C-reactive protein

A specific protein whose concentration in the blood rises in response to inflammation.

Cancer

Any disorder of cell growth that results in the invasion and destruction of surrounding healthy tissue by abnormal cells. Cancer cells arise from normal cells whose nature is permanently changed.

Carbohydrate

Type of organic compound of sugars and an essential intermediate in the conversion of food to energy. A dietary micronutrient that releases energy when metabolised in the body.

Carcinogen

Any substance or agent capable of causing cancer.

Carcinogenesis

The process by which a malignant tumour is formed.

Carcinoma

Malignant tumour derived from epithelial cells, usually with the ability to spread into the surrounding tissue (invasion) and produce secondary tumours (metastases).

Catalyse

To speed up the rate of a chemical reaction through the use of a catalyst, a substance that remains unchanged by the reaction.

Cell

Structural and functional unit of most living organisms. Can exist independently or as part of a tissue or organ.

Cell adhesion

Process whereby cells interact and attach to a surface, substrate or another cell, mediated by interactions between molecules of the cell surface. Essential for maintaining multicellular structure.

Cell cycle

The highly regulated process by which cells replicate and divide, allowing tissues to grow and remain healthy.

Cell differentiation

The process of development of cells to take on the structural and functional characteristics specific to a particular tissue. Also, the degree to which tumour cells have the structure or function of the tissue from which the tumour arose. Tumours can be described as well, moderately or poorly differentiated: well-differentiated tumours appear similar to the cells of the tissue in which they arose; poorly differentiated tumours do not. The degree of differentiation may have prognostic significance.

Cell proliferation

An increase in the number of cells as a result of increased cell division.

Cell signalling

Complex communication system that governs basic activities of cells and coordinates cell actions through bonding of ligands to receptors on the cell surface. Cells within tissue use chemicals such as cytokines, growth factors and hormones to communicate.

Cell-cycle arrest

Cessation of progress through the cell cycle at checkpoint, which halts progression into mitosis.

Checkpoint

Point in the cell cycle of eukaryotic cells at which progress can be halted if the appropriate conditions are not met.

Chemotherapeutic agent

Any chemical used to treat cancer, usually refers to antineoplastic drugs.

Chromatin

Substance of which eukaryotic chromosomes are composed. Consists of proteins (histones), DNA and small amounts of RNA in a highly condensed solenoid arrangement.

Chromosomal instability

Results from ongoing errors in chromosome segregation during mitosis resulting in whole chromosomes or parts of chromosomes being duplicated or deleted, rendering them unstable.

Chromosome

Threadlike structure found in the nucleus of animal cells composed of chromatin. Carries the genes.

Chromosome segregation

When two sister chromatids or paired homologous chromosomes separate from each other during mitosis and migrate to opposite poles of the nucleus.

Chronic

Describing a condition or disease that is persistent or long lasting.

Cofactor

Non-protein component essential for the normal catalytic activity of an enzyme consisting of organic molecules (coenzymes) or inorganic ions.

Colon

Part of the large intestine extending from the caecum to the rectum.

Colonisation sites

The first site in a different organ from which the cancer originates that metastatic tissue colonises.

CpG island

Stretch of DNA, several hundred to several thousand bases long, that is rich in dinucleotides containing the bases cytosine and guanine. The 'p' denotes a phosphodiester bond meaning the C and G residues are joined along the same strand of DNA. Abundant in the promoter region of eukaryotic genes.

Cytokines

Cell-signalling molecules that aid cell-to-cell communication in immune responses and stimulate the movement of cells toward sites of inflammation, infection and trauma.

Cytosine

A pyrimidine derivation and one of the four possible nitrogenous bases in nucleotides and nucleic acids (DNA and RNA). Base pairs with guanine.

De-differentiated

Cell or tissue that undergoes reversal of differentiation and loss of specialised characteristics.

Deoxyribonucleic acid (DNA)

The double-stranded, helical molecular chain found within the nucleus of each cell, which carries the genetic information.

Diet, nutrition and physical activity

In the CUP, these three exposures are taken to mean the following: **diet**, the food and drink people habitually consume, including dietary patterns and individual constituent nutrients as well as other constituents, which may or may not have physiological bioactivity in humans; **nutrition**, the process by which organisms obtain energy and nutrients (in the form of food and drink) for growth, maintenance and repair, often marked by nutritional biomarkers and body composition (encompassing body fatness); and **physical activity**, any body movement produced by skeletal muscles that requires energy expenditure.

Dietary fibre

Constituents of plant cell walls that are not digested in the small intestine. Several methods of analysis are used, which identify different components. The many constituents that are variously included in the definitions have different chemical and physiological features that are not easily defined under a single term. The different analytical methods do not generally characterise the physiological impact of foods or diets. Non-starch polysaccharides are a consistent feature and are fermented by colonic bacteria to produce energy and short chain fatty acids including butyrate. The term 'dietary fibre' is increasingly seen as a concept describing a particular aspect of some dietary patterns.

Differentiation

Process in development in which unspecialised cells or tissues are systemically modified and altered to achieve specific and characteristic physical forms, physiological functions and chemical properties.

DNA adduct

A chemical that binds to DNA. This distorts the DNA structure and disrupts its replication, increasing the likelihood of errors in DNA replication, subsequent mutations and possibly cancer.

DNA methylation

A process by which methyl groups are added to DNA. DNA methylation is one of several epigenetic mechanisms that regulate gene expression.

DNA methyltransferase

Enzyme that adds methyl groups to DNA (nucleic acids) so as to modify gene expression.

DNA promoter region

Segment of DNA, upstream of a gene, where RNA polymerase binds to initiate transcription.

Dominant mutation

A pattern of inheritance in which an individual will express the mutation if they have at least one copy of the mutant (or dominant) gene.

Enabling characteristic

Property a tumorous cell exhibits which facilitates the attainment and sustainment of the 'hallmarks of cancer'.

Endocrine

Referring to organs or glands that secrete hormones into the blood.

Endogenous

Substances or processes that originate from within an organism, tissue or cell.

Energy

Energy, measured as calories or joules, is required for all metabolic processes. Fats, carbohydrates, proteins and alcohol from foods and drinks release energy when they are metabolised in the body.

Enzyme

Protein that acts as a catalyst in biochemical reactions. Each enzyme is specific to a particular reaction or group of similar reactions. Many require the association of certain non-protein cofactors in order to function.

Epigenetics

Relating to the control of gene expression through mechanisms that do not depend on changes in the nucleotide sequence of DNA, for example, through methylation of DNA or acetylation of histone.

Epithelial-mesenchymal transition (EMT)

A developmental process in which epithelial cells exhibit reduced adhesion, increased cell mobility and loss of E-cadherin expression. The transition in behaviour is important in mesoderm formation and neural tube formation.

Essential nutrient

A substance that is required for normal metabolism that the body cannot synthesise at all or in sufficient amounts, and thus must be consumed.

Ethanol

An organic compound in which one of the hydrogen atoms of water has been replaced by an alkyl group. See **alcohol**.

Exogenous

Arising from outside the body.

Exposure

A factor to which an individual may be exposed to varying degrees, such as intake of a food, level or type of physical activity, or aspect of body composition.

Extracellular matrix

The material that surrounds cells in animal tissues. Contains an aqueous lattice of proteins and other molecules.

Extravasate

Allowing or forcing out a fluid, especially blood, to move from the vessel that contains it to the surrounding area.

Fat

Storage lipids of animal tissues, mostly triglyceride esters. See **adipose tissue**.

Fatty acid

A carboxylic acid with a carbon chain of varying length, which may be saturated (no double bonds) or unsaturated (one or more double bonds). Three fatty acids attached to a glycerol backbone make up a triglyceride, the usual form of fat in food and adipose tissue.

Folate

A salt of folic acid. Present in leafy green vegetables, peas and beans, and fortified breads and cereals.

Free radicals

An atom or molecule that has one or more unpaired electrons. A prominent feature of radicals is that they have high chemical reactivity, which explains their normal biological activities and how they inflict damage on cells. There are many types of radicals, but those of most importance in biological systems are derived from oxygen and known collectively as reactive oxygen species.

Functional capacity

The optimal or maximum level at which the body, organ or tissue can function.

Functional reserve

Remaining capacity of an organ or tissue to fulfil its physiological activity, especially in the context of disease, ageing or impairment.

Gene

Unit of heredity composed of DNA. Visualised as a discrete particle, occupying specific position (locus) on a chromosome, that determines a particular characteristic.

Gene expression

The manifestation of the effects of a gene by the production of the particular protein, polypeptide or type of RNA whose synthesis it controls. The transcription of individual genes can be 'switched on' or 'switched off' according to the needs and circumstances of the cell at a particular time.

Genetic code

Means by which genetic information in DNA is translated into the manufacture of specific proteins by the cell. Represented by codons, which take the form of a series of triplets of bases in DNA, from which is transcribed a complementary sequence of codons in messenger RNA. The sequence of these codons determines the sequence of amino acids during protein synthesis.

Genome-wide association studies (GWAS)

Association study in which numerous genetic variants across the genome are analysed to measure differences associated with a trait, disease, or phenotype.

Genomic instability

Abnormal rate of genetic change in a cell population which becomes evident as proliferation continues.

Genotoxic

Referring to chemical agents that damage the genetic information within a cell, causing mutations, which may lead to cancer.

Germ-line mutation

A mutation occurring in reproductive cells or their precursors that may be transmitted to the organism's descendants.

Glucose

A six-carbon sugar, the main product of photosynthesis, that is a major energy source for metabolic processes. It is broken down by glycolysis during cellular respiration.

Growth factors

Various chemicals, particularly polypeptides, that have a variety of important roles in the stimulation of cell growth and replication. They bind to cell surface receptors.

Guanine

A purine derivative and one of the four possible nitrogenous bases in nucleotides and nucleic acids (DNA and RNA). Base pairs with cytosine.

Guanosine

A nucleoside consisting of one guanine molecule linked to a ribose sugar molecule in DNA.

Haem

The part of the organic molecule haemoglobin in red blood cells containing iron to which oxygen binds for transport around the body.

Hallmarks of cancer

Key phenotypic characteristics in structure and function that represent an essential part of the biology of a cancer cell.

Histones

Family of proteins held in complexes with DNA in eukaryotic chromatin and chromosomes. Involved in the condensation and coiling of chromosomes during cell division. Chemical modification of histones (methylation and acetylation) is key in suppressing or activating gene activity.

Homeostasis

Regulation of an organism's internal environment within a controlled range so that physiological processes can proceed at optimum rates.

Hormone

A substance secreted by specialised cells that affects the structure and/or function of cells or tissues in another part of the body.

Hyperinsulinemia

High blood concentrations of insulin.

Hypermethylation

An epigenetic control that leads to gene inactivation in cancer cells by adding methyl groups to DNA sequences, inactivating most important cellular pathways.

Hypomethylation

The loss of the methyl group or the unmethylated state of a site that is normally methylated in DNA sequences. Occurs in mostly repeated sequences and is prevalent in cancer cells as it helps these cells adapt to the tumour microenvironment during metastasis.

Immune system

Complex network of cells, tissues and organs that work together to defend against external agents such as microorganisms.

In vitro

Processes that occur outside the body, in a laboratory apparatus.

In vivo

Describing biological processes as they are observed to occur within living organisms.

Incidence

Frequency of occurrence of new cases of a disease in a particular population during a specified period.

Inflammation

The immunologic response of tissues to injury or infection. Inflammation is characterised by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, pain, heat and swelling. Inflammation may be acute (such as in response to infection or injury) or chronic (as part of several conditions, including obesity).

Insulin

A protein hormone secreted by the pancreas that promotes the uptake and utilisation of glucose, particularly in the liver and muscles. Inadequate secretion of, or tissue response to, insulin leads to diabetes mellitus.

Insulin-like growth factor (IGF)

Polypeptides with high sequence similarity to insulin that are part of a complex system that cells use to communicate with their physiologic environment. IGF-I is the main mediator of growth hormone activity.

Insulin-like growth factor binding proteins (IGFBPs)

A family of proteins that bind to and transport specific IGFs (see **insulin-like growth factor**) in the circulation. Most circulating IGFs are bound to IGFBPs.

Intracrine

Denoting self-stimulation through cellular production of a factor that acts within the cell.

Invasion

Movement of one cell type into a territory normally occupied by a different cell type.

Ionising radiation

Radiation of sufficiently high energy to cause ionisation in the medium through which it passes. May consist of a stream of high-energy particles (electrons, protons, alpha-particles) or short-wavelength electromagnetic radiation (ultraviolet, X-rays, gamma-rays). It can cause extensive damage to the molecular structure of a substance.

KRAS gene

Provides instructions for making the K-Ras protein, which is involved in cell signalling pathways, cell growth, cell maturation and cell death. Mutated forms are associated with some cancers.

Macronutrient

The components of the diet that provide energy: protein, carbohydrate and fat.

Macrophage

Large phagocytic cell forming part of the body's immune system. It can ingest pathogenic microorganisms or cell debris.

Malignant

A tumour with the capacity to spread to surrounding tissue or to other sites in the body.

Mendelian randomisation

A method of using measured variation in genes of known function to mimic a potential causal effect of a modifiable exposure on disease. The design helps to avoid problems from reverse causation and confounding.

Menopause

The cessation of menstruation.

Messenger ribonucleic acid (mRNA)

RNA molecule responsible for carrying the genetic code transcribed from DNA to specialised sites within the cell (known as ribosomes), where the information is translated into protein composition.

Meta-analysis

The process of using statistical methods to combine the results of different studies.

Metabolism

The sum of chemical reactions that occur within living organisms.

Metabolites

Various compounds that take part in or are formed by chemical, metabolic reactions.

Metastasis/metastatic spread

The spread of malignant cancer cells to distant locations around the body from the original site.

MicroRNA (miRNA)

Small RNA molecule that binds to target mRNA molecules and suppresses the translation of mRNA into the protein, thereby silencing gene expression.

Mitogen-activated protein kinase (MAPK) pathway

A chain of proteins that transmits chemical signals from outside the cell to the cell's nucleus to activate transcription factors that control gene expression.

Mitogenic

Referring to a chemical substance that encourages a cell to divide, by triggering mitosis. Mitogens are usually proteins. Mitogenesis is the induction (triggering) of mitosis, typically through a mitogen.

Mutation

A permanent change in the nucleotide sequence of the genome (an organism's complete set of DNA).

Neoplastic

Referring to abnormal new growth of tissue that persists in the absence of the original stimulus.

Neutrophils

A type of white blood cell that fights infection by ingesting microorganisms and releasing enzymes that kill microorganisms.

Non-communicable diseases (NCDs)

Diseases which are not transmissible from person to person. The most common NCDs are cancer, cardiovascular disease, chronic respiratory diseases, and diabetes.

Nucleotide

Organic compound consisting of a nitrogen-containing purine or pyrimidine base linked to a sugar (ribose or deoxyribose) and phosphate group.

Nutrient

A substance present in food and required by the body for maintenance of normal structure and function, and for growth and development.

Nutrition

Process by which organisms obtain energy and nutrients (in the form of food and drink) for growth, maintenance and repair.

Obesity

Excess body fat to a degree that increases the risk of various diseases. Conventionally defined as a BMI of 30 kg/m² or more. Different cut-off points have been proposed for specific populations.

Oestradiol

The principal female sex hormone produced mainly by the ovaries before menopause and by adipose tissue after. It promotes the onset of secondary sexual characteristics and controls the menstrual cycle.

Oestrogen

The female sex hormones, produced mainly by the ovaries during reproductive life and also by adipose tissue.

Oncogene

Dominant mutant allele of a cellular gene that disrupts cell growth and division and is capable of transforming a normal cell into a cancerous cell.

Oxidative stress

Overproduction of reactive oxygen species that may damage tissues.

Paracrine

Type of cell signalling in which the target cell is close to the cell releasing the signal. Paracrine signals include neurotransmitters and neurohormones.

Peptide

Any group of organic compounds comprising two or more amino acids linked by peptide bonds.

Phase I metabolising enzyme

Enzymes in the first phase of detoxification (modification) that introduce reactive and polar groups.

Phase II metabolising enzyme

Enzymes in the second phase of detoxification (conjugation) that conjugate active substances from phase one to charged species that are more easily excreted, for example, in bile.

Phenotype

The observable characteristics displayed by an organism; depends on both the genotype (the genetic makeup of a cell) and environmental factors.

Phosphatidylinositol 3-kinase (PI3K) pathway

Pathway essential for the normal development of many parts of the body. This signalling pathway influences many critical cell functions, including the synthesis of new proteins, cell growth and division (proliferation), and cell survival.

Physical activity

Any movement using skeletal muscles that requires more energy than resting.

Phytochemical

Non-nutritive bioactive plant substances that may have biological activity in humans.

Pooled analysis

In epidemiology, a type of study in which original individual-level data from two or more original studies are obtained, combined and re-analysed.

Prevalence

The total number of individuals who have a characteristic, disease or health condition at a specific time, related to the size of the population, for example, expressed as a percentage of the population.

Proliferation

Increase in the number of cells, for example, in a tissue.

Protein

Polymer of amino acids linked by peptide bonds in a sequence specified by mRNA with a wide variety of specific functions including acting as enzymes, antibodies, storage proteins and carrier proteins.

Proto-oncogene

Gene involved in regulation of cell proliferation which, if mutated or overexpressed, has the capacity to cause oncogenesis.

p53

A protein central to regulation of cell growth. Mutations of the p53 gene are important causes of cancer.

Reactive nitrogen species (RNS)

Nitrogen-containing radical species or reactive ions, such as nitric oxide (NO) and peroxynitrite (ONOO-), which are able to damage DNA, such as by inducing DNA strand breaks or base modifications.

Reactive oxygen species (ROS)

Oxygen-containing radical species or reactive ions that can oxidise DNA (remove electrons), for example, hydroxyl radical (OH⁻), hydrogen peroxide (H₂O₂) or superoxide radical (O²⁻).

Receptor

Protein on the surface of a cell that binds to a circulating substance (ligand) to initiate the transmission of messages to the inside of the cell.

Recessive mutation

A pattern of inheritance in which an individual expresses the mutation only if both copies of the gene are mutant.

Regulatory region

DNA sequence upstream of a coding region to which molecules such as transcription factors bind and regulate gene expression.

Resilience

Property of a tissue or of a body to resume its former condition after being stressed or disturbed.

Retinoid

Compounds chemically related to or derived from vitamin A. They may be used for treatment of some cancers.

Single nucleotide polymorphisms (SNPs)

Variation in the base sequence occurring at a given single position or nucleotide in the genome, found in more than 1 per cent of the population. This is the most common form of genetic variation among people.

Stem cell

Cell that is not differentiated but can undergo unlimited division to form other cells, which can either remain stem cells or differentiate to form specialised cells.

Steroid hormones

Group of structurally related hormones synthesised from cholesterol that control various physiological functions.

Stress

A state of physiological or psychological strain caused by adverse stimuli that tends to disturb the functioning of an organism.

Stromal cells

Connective tissue cells of an organ.

Substrate

Substance upon which an enzyme acts in biochemical reactions; basic chemical building block of biochemical pathways.

System

Set or series of interconnected or interdependent cells or organs that act together in a common purpose or produce results impossible to achieve by the action of one alone.

Systemic

Describing something that occurs throughout the body, not just locally.

Telomeres

Region of repetitive DNA at the end of a chromosome, which protects it from destruction during DNA replication.

Thymine

A pyrimidine derivative and one of the four possible nitrogenous bases in nucleotides and nucleic acids (DNA and RNA). Base pairs with adenine.

Tissue

A collection of one or more types of cells of similar structure organised to carry out particular functions.

Transcription

The process in living cells in which the genetic information of DNA is transferred to a molecule of messenger RNA (mRNA) as the first step in protein synthesis. Takes place in the cell nucleus or nuclear region and is regulated by transcription factors.

Transcription factor

Any group of proteins that work synergistically to regulate gene activity by increasing or decreasing the binding of RNA polymerases to the DNA molecule during transcription.

Translate

Process in living cells in which the genetic information encoded in mRNA in the form of a sequence of nucleotide triplets (codons) is translated into a sequence of amino acids in a polypeptide chain during protein synthesis. Takes place in ribosomes in the cell cytoplasm.

TP53

Protein that acts as a tumour suppressor, which means it regulates cell division by keeping cells from growing and dividing (proliferating) too quickly or in an uncontrolled way. TP53 is the most commonly mutated gene in human cancer.

Tumorigenesis

The process of tumour development.

Tumour

A mass of neoplastic and other cells.

Tumour suppressor gene

A gene that protects a cell from one step on the path to cancer. When this gene mutates to cause a loss or reduction in its function, the cell can progress to cancer, usually in combination with other genetic changes.

Visceral obesity

Form of obesity due to excessive deposition of fat in the omentum and around the abdominal viscera, rather than subcutaneously (peripheral obesity). Poses a greater risk of diabetes mellitus, hypertension, metabolic syndrome and cardiovascular disease than peripheral obesity.

Vitamin

One of a number of organic compounds required from food or drink by living organisms in relatively small amounts to maintain normal structural function.

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Our Cancer Prevention Recommendations

Be a healthy weight

Keep your weight within the healthy range and avoid weight gain in adult life

Be physically active

Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans

Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of ‘fast foods’ and other processed foods high in fat, starches or sugars

Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat

Eat no more than moderate amounts of red meat, such as beef, pork and lamb.
Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks

Drink mostly water and unsweetened drinks

Limit alcohol consumption

For cancer prevention, it’s best not to drink alcohol

Do not use supplements for cancer prevention

Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can

Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can

Check with your health professional what is right for you

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

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