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GENERAL CONCEPTS OF CANCER AND NUTRITION: DIET, BODY COMPOSITION AND PHYSICAL ACTIVITY AND THEIR RELATIONSHIP WITH THE CANCER PROCESS

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Índice

Presentation

Hello, I'm very happy to present you this course. It's about a very important and pressing issue: nutrition and cancer.

This is an online course that is structured in modules.

Module 1 starts by presenting in detail the key concepts and definitions that underlie the development of the oncological disease. Specifically, it will describe the carcinogen process, the development of neoplastic cells, the causes for cancer and the development of this disease.

Then, it'll analyse in detail the specific connections between food items of vegetable or animal origin or another origin and the incidence of different types of cancer in order to determine the real connection between our diet, our food habits and cancer.

Finally, in item 5 of module 1, we'll point out the connection between other nutritional variables, other variables related to nutrition, such as obesity, physical activity or sedentariness.

Today, we know there is a connection between these elements and cancer.

They're known to be risk factors or preventive factors for several types of oncological diseases.

I'm sure this course will boost your scientific knowledge and it will also distinguish you professionally in this important field: nutrition and cancer.

Keep up the good work and enjoy.

Overview of cancer and nutrition

The cancer process

Questions in general terms

This unit is an introduction to the whole process of cancer and its link to nutrition. We will try to address the following questions in very general terms:

- What is cancer? How cancer develops from normal cells.
- What are the established causes of cancer?
- Why dietary and other nutritional factors could be a cause of cancer.
- How nutritional components influence the cancer process.
- How do we determine that a specific food or nutrient causes (or protects from) cancer?
- How do we use the available evidence to make an overall judgement about the causal link between specific nutritional factors and cancer?

The formation of a cancer

The formation of a cancer is a long and complex process by which tumor cells overcome and evade the multiple control mechanisms established in the human body.

Although cancer is often considered as a single entity, it actually encompasses a broad group of diseases affecting different organs or tissues. Even tumors arising from the same tissue are increasingly recognised as comprising several subtypes. Nevertheless, all of them have common features, namely: they are characterized by uncontrolled growth and dissemination of cells due to failures in genetic and epigenetic mechanisms.

Hallmarks of cancer

The main characteristics of cancer are defined by the capabilities acquired by tumor cells that ultimately lead to the development of tumors in humans.

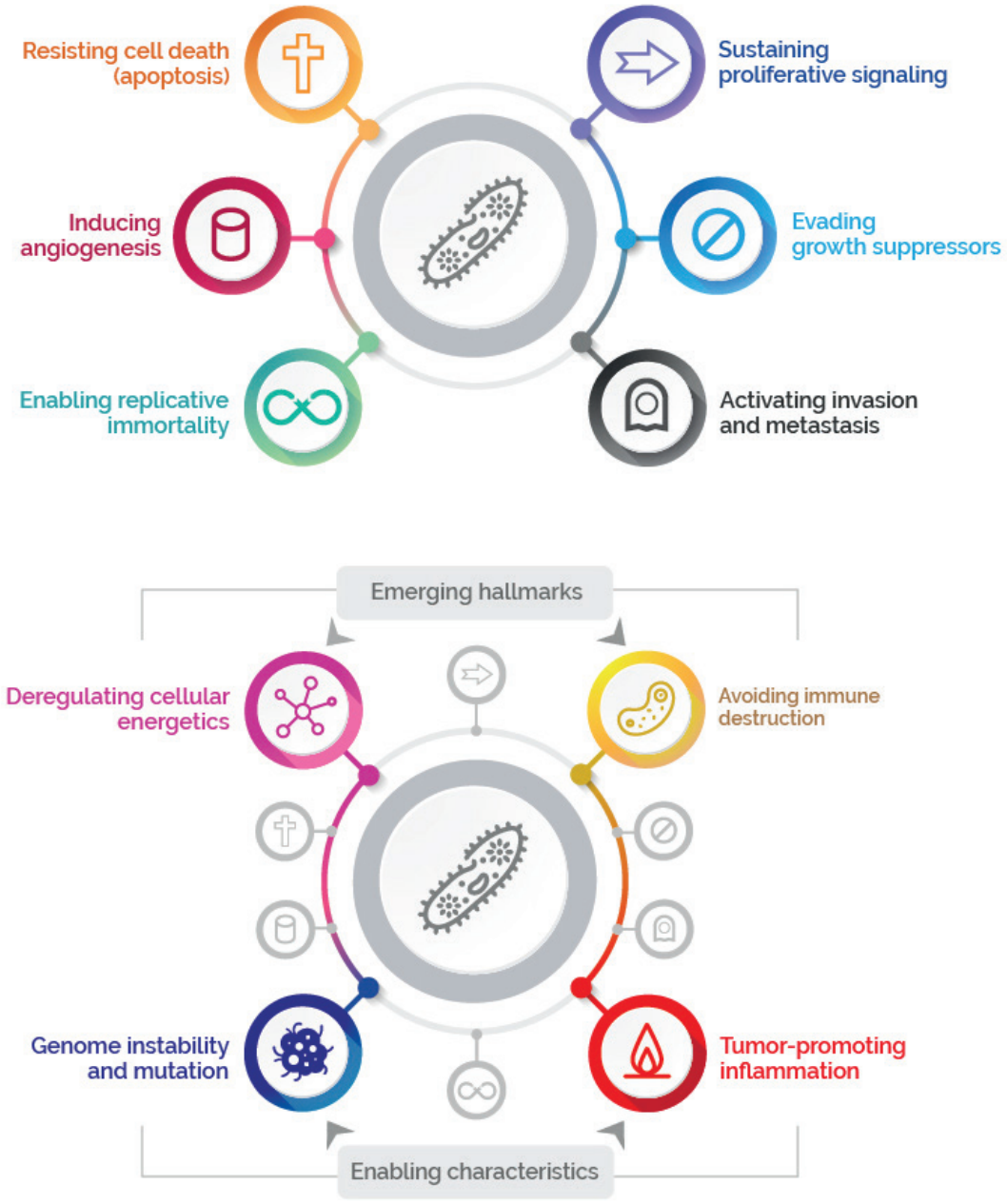
Let's go over the various hallmarks of cancer:

- The ability to maintain chronic **cell growth and proliferation**.
- The ability to **evad**e the action of multiple **suppressor genes** that limit and regulate cell growth.
- The ability to **evade** the mechanisms of the **immune system** that would destroy the incipient tumor cells.
- The acquisition of unlimited replicative potential and the capacity to delay or avoid senescence.
- **Chronic inflammation**, with increased production of inflammatory mediators with tumor-promoting effects.
- Activation of mechanisms that allow for the invasion of other tissues and which help to form **metastases** (that is the tumor nestingin tissues other than the original).
- The capacity to generate blood vessels that allow the tumor to be fed.
- Increased tendency to acquire mutations due to dysfunctions in the process of maintaining the genome.
- The ability to resist programmed cell death and
- The ability to **reprogram** the cellular energy **metabolism**.

It is worth noting that this process can be long; It may take decades from the time that a healthy cell first begins to transform, until the time when a clinically detectable tumor is present.

Emerging Hallmarks and enabling characteristics

Hallmarks of cancer



Source: Hanahan D & Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell 2011;144:646-674.

The upper side of the figure encompasses the **six hallmark** capabilities originally proposed. On the lower side, two additional hallmarks of cancer are shown that are based on more recent evidence (labelled as **emerging hallmarks**): one involves the ability to modify or reprogram cellular metabolism in order to most effectively support neoplastic proliferation, while the second allows cancer cells to evade immunological destruction, in particular by lymphocytes, macrophages, and natural killer cells. Additionally, two characteristics of neoplasia facilitate acquisition of both core and emerging hallmarks. **Genomic instability** and thus, mutability, bestow cancer cells with genetic alterations that drive tumor progression. **Inflammation** designed to fight infections and heal wounds can result in their support of multiple hallmark capabilities, thereby manifesting tumor-promoting consequences following inflammatory responses.

The causes of cancer

A risk factor

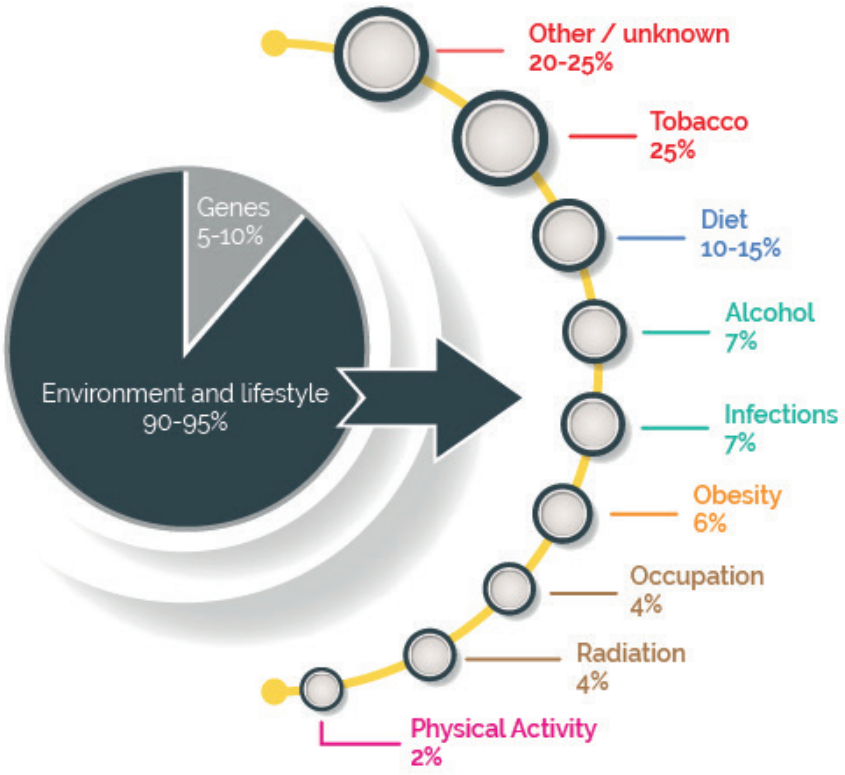
The modern concept of causality in medicine and other sciences does not correspond to the concept of deterministic cause as commonly used in plain language. Under a probabilistic framework a cause is any circumstance that, beyond reasonable doubt, modifies the probability of occurrence (risk) of a disease; it is often termed a **risk factor**.

Although the cancer process ultimately affects the genes, they are neither the sole nor the most significant cause of cancer. Only approximately 5-10% of tumors are directly attributable to hereditary or genetic factors, while the majority of the causal factors of cancer relate to the environment and lifestyle, including diet, tobacco and alcohol consumption, obesity, and infectious agents

> Most of these factors are modifiable, hence cancer is mostly preventable.

On the other hand, it must be kept in mind that cancer is a multi-causal disease and very few tumors (if any) originate exclusively from a single factor. An estimate of the proportion of cancer cases attributable to genes as well as environmental and lifestyle factors is shown in the figure below.

Proportion of cancer cases attributable to genetic, environmental, and lifestyle factors.



Source: Own production; elaborated with data from several European countries (including Spain and France), as well as from the USA and Canada.

Nutrition and cancer

It is currently taken for granted that there is a relationship between diet and cancer. However, we could ask ourselves whether such a relationship actually exists; or more specifically **might dietary factors cause cancer?** Indeed, it is easy to guess or even accept that certain elements that are essentially harmful to living beings include, among their effects, the induction of cancer. This would be the case, for instance, for ionizing radiation; some chemicals or environmental contaminants, such as asbestos; and, of course, the many carcinogenic compounds contained in tobacco smoke. But diet (**what we eat**) is, in essence, something necessary for life; so, again, why would it have a carcinogenic effect?

To understand this, it is essential to first explain the cancer process, as has been done in the previous section. Furthermore, it is also necessary to understand the complexity that encompasses the concepts covered under the terms 'diet' and 'nutrition'. So far, we have used them as synonyms or interchangeable concepts. However, it is time to clarify their precise meaning and their use in the context of this course, as well as within the overall framework of research on cancer and nutrition.

> Nutrition is the set of integrated processes by which living beings acquire the energy and nutrients needed to maintain their structure and to function normally.

All the **nutrients** and **energy** needed for the chemical reactions that are essential for maintaining life come from the **diet**: some are provided as essential nutrients, while others are synthesized by the body from dietary components. Substances that derive from diet which are not necessary for metabolism are not considered as nutrients, although they influence metabolic processes; these include both substances useful for physiological functions as well as harmful compounds.

¿Did you know...

Being physically active leads to metabolic changes that promote health.
Some of the benefits derived from physical activity include a reduction in the susceptibility to suffer from specific tumors.

Excess energy intake that does not get balanced by physical activity leads to a positive energy balance which is stored as fat, and ultimately leads to higher **body fatness**.

From now on, when we use the term **nutrition** this will include the integrated processes linking dietary intake, physical activity and body fatness.

Since diet, body composition, and physical activity are all essential aspects of life, an imbalance and inappropriate levels of these factors can disturb normal homeostasis. Nutrition may influence cancer risk in a range of different ways. Some foods, for instance,may be vectors for specific substances that act as particular carcinogens at particular sites.

However, taking into account the main features of the cancer process and of nutritional factors, it is clear that it is not the single or acute exposure to a factor -such as consumption of a food on a specific day- that matters, but it is rather the regular exposure to a specific dietary pattern, or to a level of physical activity that matters.

Nutrition and cancer

Diet, nutrition, physical activity and body composition

> There is growing evidence on how diet, body fatness and physical activity can have an impact on the biological mechanisms that may influence cancer risk by linking them to specific hallmarks of cancer

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

Nutrition and the hallmarks of cancer

Source: World Cancer Research Fund & American Investigation of Cancer Research, Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018. Adapted from: Cell 2011;144:646-674.

The influence of technology on research

> Many advances in science, and particularly in medicine, come from previous advances in technology.

As the application of complex techniques has become easier and cheaper, new experimental studies in animal models and cell lines have multiplied. The data from these studies are of great value, indeed.

However, experimental studies, although essential for establishing the basis of many hypotheses and new discoveries, are not sufficient alone in order to establish the causal relationship between a factor and a disease in humans. A final step is always needed to prove the evidence of such a relationship in human beings.

The branch of medicine that addresses the role of health and disease determinants in human populations is **epidemiology**. Since experimentation with humans is not allowed, with very limited exceptions, most epidemiological evidence is predominantly **observational**.

Given its importance, it is worth explaining the reasoning behind epidemiology to establish causal relationships in medicine and, specifically, in the field of cancer and nutrition.

Judging the evidence: the approach

> The purpose is to identify what causes (or what protects from) cancer with sufficient confidence to support a recommendation regarding the imputed cause (or protective factor).

As already mentioned, much of the evidence on nutrition and cancer is observational, although it is often reinforced by extensive experimental data. Since there is no perfect way to establish causality with the available evidence, a rigorous and systematic approach is needed to make sound and reliable judgements. We shall briefly describe some key elements of this approach.

Who	How	What
Usually, the judgement is made by a highly skilled panel of experts with expertise on the given topic; it must also include members who have expertise on this approach and knowledge of the rules to be applied during the panel's discussion.	The methodology and rules must be explained and made transparent, so that they can be accessed and challenged. This includes the amount of evidence to be assessed, the selection of which must have been done systematically while following standard procedures.	Nowadays, these evaluations are never based upon results from a single study, even if it is an outstanding and excellent piece of work, but on the accumulation of evidence from several studies, that must be considered on their own individual values and together with other studies.

When reading systematic reviews, one of the key points is to determine how the authors assessed causality:

- Type of study (design)

  A **randomized controlled trial (RCT)** is considered to be the gold standard for assessing the effect of a factor on a given outcome. However, RCTs on the effect of dietary or physical activity interventions on the risk of cancer are scarce owing to feasibility and limitations: these RCTs are usually long, expensive, and logistically complex.

  Prospective studies (cohort studies), despite the intrinsic limitations of their observational design, possess some good properties: measurements can be taken prior to cancer diagnosis (mainly important for biomarkers), and allow for long follow-up periods multiple outcomes.

  Case-control studies, the retrospective alternative (quicker and cheaper) to cohort studies, are much more prone to bias (distorted results). Some of these biases (i.e. errors in measurement of the exposure) are particularly relevant to diet and nutrition, especially when biomarkers are needed.

  Other **epidemiological studies (descriptive, cross-sectional, ecological)** merely contribute towards the generation of hypotheses or reinforce conclusions from interventional or prospective studies.

- Quality of the study

  In spite of its favourable features, RCTs and prospective studies are not all of equal value. The major determinant of the quality (or value) of a study is its **internal validity**, reflecting that the study has actually been well designed, conducted and analysed. A key issue when dealing with causality is the assessment of **confounding**, or how we are reasonably sure that the observed (causal) link between obesity and breast cancer, for instance, is not explained by other factors that can be linked to both obesity and breast cancer. In general, this is easily solved in RCTs because the potential confounders are evenly distributed in the intervention and control group thanks to randomization. However, this is much more complex in a cohort or case-control study; proper assessment of confounding is crucial for assessing causality when the judgement comes from an observational design.

- Experimental evidence

  A comprehensive judgement that a given nutritional factor causes or protects against cancer requires some evidence about the mechanisms that explain why this might happen (biological plausibility). Most studies on mechanisms tend to derive from animal studies, but a preference must be given to human studies when available. Although the judgement of evidence is mainly based upon epidemiological studies, good studies on mechanisms are of great value in supporting and reinforcing a causal link.

World Cancer Research Fund

Keeping in mind previous considerations, different institutions, research groups and panels have established guidelines and grading criteria when it comes to judging the evidence. In this course we will mostly, although not exclusively, use those established by the World Cancer Research Fund. Specifically, in the following units we will focus upon nutritional factors with 'strong' evidence of causal relationships with cancer. The criteria for a body of evidence to be considered as 'strong', which in turn includes the two grades of 'convincing' and 'probable' are presented in Box 1.

Box 1. Criteria for grading evidence for cancer prevention

Convincing
(Strong evidence)

These criteria are for evidence strong enough to support a judgement of a convincing causal relationship, which **justifies goals and recommendations** designed to reduce the incidence of cancer. A convincing relationship should be **robust enough to be highly unlikely to be modified in the foreseeable future** as new evidence accumulates.

All of the following were generally required:

- Evidence from **more than one study type**.
- Evidence from **at least two independent cohort** studies.
- **No substantial unexplained heterogeneity** within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- **Good quality** studies to **exclude** with confidence the possibility that the observed association results from **random or systematic error**, including **confounding, measurement error, and selection bias**.
- Presence of a **plausible biological gradient** ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure so long as this can be explained plausibly.
- **Strong and plausible experimental evidence**, either from human studies or relevant animal models, that typical human exposure can lead to relevant cancer outcomes.

Probable

(Strong evidence)

These criteria are for evidence strong enough to support a judgement of a probable causal relationship, which **would generally justify goals and recommendations** designed to reduce the incidence of cancer.

All the following were generally required:

- Evidence from **at least two independent cohort studies**, or **at least five case-control studies**.
- **No substantial unexplained heterogeneity** between or within study types in the presence or absence of an association, or direction of effect.
- **Good quality** studies to **exclude** with confidence the possibility that the observed association results from **random or systematic error**, including **confounding, measurement error, and selection bias**.
- Evidence for **biological plausibility**.

Source: World Cancer Research Fund & American Investigation of Cancer Research, Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018.

To find out more...

Many studies suggest an association between a nutritional factor and a type of cancer, but the evidence is still inadequate to support a probable or convincing causal relationship (not meeting Box 1 criteria). In these cases, the evidence is considered to be 'limited' and is not sufficient to establish recommendations. When the evidence is not strong enough to support a probable or convincing causal relationship, but is suggestive of a direction of effect, the evidence is defined as limited-suggestive.

Judging the evidence: uncertainty and limitations

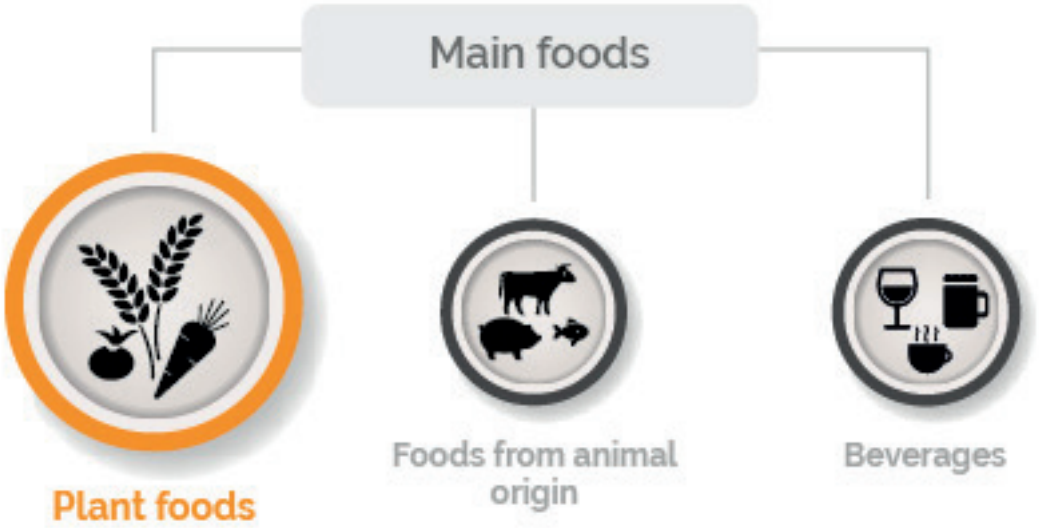
A final thought must be given to recalling that scientific knowledge is not static; fortunately, on the contrary, it moves and in some fields it moves very fast. The available evidence is imperfect: although our conclusions derive from the best evidence available now, which reflects past and recent research priorities and has been synthesised and judged in a rigorous way, the evidence presented offers an incomplete picture. However, we are confident that there is a body of consolidated, soundly based knowledge, which will be the subject of this course.

A food-based approach to assess the relationship between diet and cancer

Plant foods

Introduction

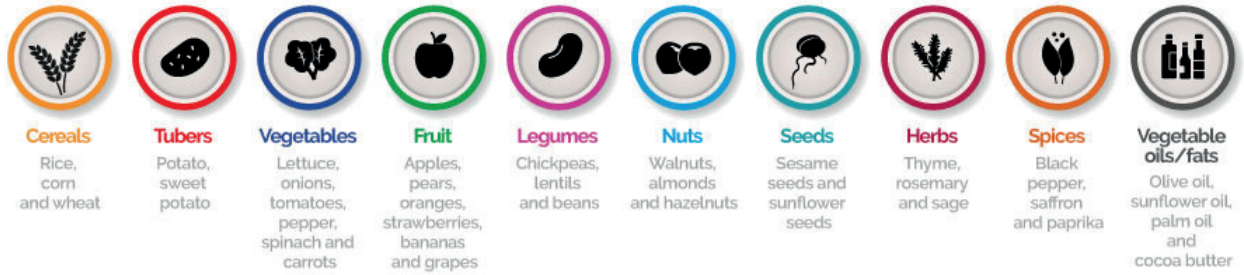
Many different approaches can be taken when assessing the relationship between diet and cancer. For instance, the focus can be placed on nutrients, macronutrients or groups of bioactive compounds. Since the most natural and straightforward way to describe diet is by considering what people actually eat (foods), we have taken a **food-based** approach. In the next three units we have grouped main foods in three major categories: plant foods, foods from animal origin, and beverages. For each of them we will first review how specific food groups are defined in epidemiology and cancer research, which are their nutritional properties, and finally, we will summarize the evidence for each food group in relation to cancer.



General definition and major groups

Plant-derived foods can be grouped according two main categories: botanical and culinary. Botanical definitions are more precise but culinary definitions are more easily understood because they are based on composition, and cultural and culinary uses of foods. For the purposes of this course, plant-based foods are categorised according to culinary definitions.

The culinary term "plant foods" refers to the edible parts of a plant, tree, bush or vine (e.g., leaves, roots, tubers, bulbs, stems, stalks, flowers, fruits and grains) and usually includes fungi (mushrooms and truffles) and algae. This group basically includes:



The composition of plant foods depends on both species and subtype, as well as on climate, soil, agricultural practices, ripeness, and processing and storage conditions. Plant foods are usually rich sources of dietary fiber, several vitamins (vitamin C, folate and carotenoids) and minerals (magnesium, potassium), and phytochemicals (such as polyphenols, glucosinolates, alkaloids, terpenes, etc.), and are low in fats, especially saturated fats.

Plant foods may be contaminated during the storage, thermal processing, cooking, and preservation. All these processes may lead to the production of substances with potential toxic effects, including carcinogenicity. However these substances are not natural components of the plant-derived foods.

Description of plant foods

- Cereals

  Cereals, or grains, are the seeds and energy stores of cultivated grasses. The main types are wheat, rice, corn, millet, sorghum, barley, oats, and rye. Wholegrains are grains and grain products made from the whole grain seed, usually called the kernel, which consists of the bran, germen and endosperm. Many of the grains that we consume are refined (such as white rice, bread, or pasta). Grains are first broken into pieces and then refined, removing the bran, germ and, usually, the aleurone layer. Refined grains are considered easier to cook and chew than wholegrains; are light in color (which is attractive to many consumers); have a longer shelf-life than wholegrain products (as the oil in bran goes rancid relatively quickly); and cost less.

The endosperm is the biggest part of the grain and is rich in starches, which account for around 70% of its raw weight. The germ is the smallest part of the grain and contains oils, fiber and proteins. The outer parts of the grain are the bran and the aleurone layer, which is the outermost layer of the endosperm, and are especially rich in fiber. Cereals also contain variable amounts of protein, polyunsaturated fatty acids, B vitamins, vitamin E, iron, and various trace elements, as well as phytochemicals. The refining process removes most of the fiber, oil, and B vitamins, as well as approximately 25% of the protein, as these are most concentrated in the germ and in the outer layers of the grain. Wheat, barley and rye contain gluten (a mixture of proteins that triggers coeliac disease in gluten-sensitive subjects). Processed grains have a higher glycaemic index than unprocessed grains and, generally, the greater the degree of processing, the greater the glycaemic index.

- Tubers

  Tubers, or starchy vegetables, are enlarged underground structures in some plant species used as storage organs for nutrients. They include potatoes, sweet potatoes, cassava and taro. They are less concentrated sources of starch than grains, although this content varies from 15 to 30%.

- Legumes

  Legumes, or pulses, are the edible, nutritious seeds in the form of pods of the Leguminous plants. Legumes include beans, lentils, chickpeas, peas, broad beans, and soya beans. The dried forms, which have matured and dried on the plant, are eaten most widely. But some varieties are eaten as a green vegetable, such as peas. Dried legumes are typically high in carbohydrates, fiber, protein, B vitamins, minerals (iron, copper, magnesium, manganese, zinc, and phosphorous) and phytochemicals (polyphenols) and generally low in fat. Soy is known for its high isoflavone content, a bioactive subclass of polyphenols, which have estrogenic activities.

- Vegetables

  Vegetables are the edible parts of plants, including fungi and algae. Vegetables are usually classified according to which part of the plant is eaten. They can have edible leaves (cabbage, lettuce, spinach), roots (carrot, radish, turnip), bulbs (onion, garlic, leak), steams and stalks (asparagus, celery), and flowers (artichoke, cauliflower, broccoli). Other parts of plants that are used as vegetables include some grains (sweetcorn), fresh pods (green beans), and fruits (tomatoes, courgettes and aubergines). Vegetables can be eaten either raw or cooked and

play an important role in human nutrition, due to being mostly low in energy, fat and carbohydrates, but high in vitamins (carotenoids, B vitamins, vitamin C, and vitamin K), minerals (calcium, magnesium, potassium, and iron), dietary fiber and phytochemicals (polyphenols, glucosinolates, etc.). Vegetables can also be preserved, through salting, drying, fermenting or pickling. Pickling is the addition of brine (a concentrated salt solution), vinegar, soy sauce or a spicy solution to preserve and give a different and appreciated flavour. Some vegetables may also be fermented during pickling. These types of preserved vegetables are mainly consumed in East Asia. Botanically, cruciferous vegetables are vegetables of the Brassicaceae family, and include cabbages, broccoli, cauliflower and Brussels sprouts. They are good sources of the phytochemicals glucosinolates and their products, isothiocyanates and indoles.

- Fruits

  Fruits are the edible part of a plant, tree, bush, or vine that contains seeds and pulpy surrounding tissue and has a sweet or tart flavour. Fruits can be classified culinarily as pomes (apples, pears, and quince), drupes or stone fruits (cherries, peaches, apricots, plums), citrus fruits (oranges, lemons, mandarins, grapefruits), berries (grapes, strawberries, blueberries, blackberries), melons (melons, watermelons), tropical fruits (bananas, pineapples, papayas, pomegranates). Fruits are low in calories and fat and are a good source of simple sugars, fiber, vitamins, and phytochemicals (polyphenols).

- Nuts and sedes

  Nuts are edible seeds surrounded by a tough, dry shell. This definition includes true nuts (such as hazelnuts and chestnuts), as well as seeds that most people think of as nuts (including Brazil nuts, macadamia nuts, and cashews). Other seeds commonly eaten include sunflower, sesame, pumpkin, and poppy seeds. Peanuts are botanically classified as legumes, but in cuisine they are classified as nuts. Nuts and seeds are rich in energy, protein, polyunsaturated and monounsaturated fats, fiber, vitamins (vitamin E, vitamin B2, folate), minerals (magnesium, phosphorus, potassium, and selenium), and phytochemicals (polyphenols).

- Herbs and spices

  Herbs are usually the fresh or dry leaves or whole plant, while spices come from other parts of the plant, such as the seeds, and are usually dried. Many different parts of plants are used as herbs or spices, such as the leaves (sage, bay, or basil), stems (ginger, lemongrass), bark (cinnamon), rhizomes (ginger), roots (horse-

radish), flower buds (cloves), stamens (saffron), seeds (mustard, cumin), kernels (nutmeg), and fruits (peppers). Herbs and spices contain large amounts of bioactive phytochemicals (polyphenols, terpenoids, isothiocyanates), which provide their characteristic color, aroma and taste (flavour).

- Vegetable oils

  Fats and oils are the most energy-dense constituents of diets. Oils can be classified according to their source, use, or chemical composition. Those that are semisolid at ambient temperature are relatively high in saturated fatty acids, such as palm and coconut oils, which are semisolid in temperate climates but liquid in the tropics. Those that are liquid at room temperature are generally high in mono- and/or poly-unsaturated fatty acids. Plant oils are extracted from oily fruits (such as olives), seeds (such as rape and sunflower), nuts (such as walnuts), and other sources, such as legumes (soy oil). A small amount of dietary fat is necessary to provide the essential fatty acids that cannot be made by the body. Linoleic acid (C18:2) and alpha-linolenic acid (C18:3) are the two essential fatty acids, and are found in nuts and seed oils. Olive oil is rich in monounsaturated fatty acid (oleic acid, C18:1). Margarine is made from plant oils that are converted into saturated fats by a process called hydrogenation, which partially or completely removes or reconfigures the double bonds of plant oils, but leads to the production of trans-fatty acids.

Findings from epidemiological and mechanistic studies

Table 1 summarizes the findings from epidemiological and mechanistic studies on the causal relationships between plant-derived foods and cancer risk by location.

Table 1 summarizes the findings from epidemiological and mechanistic studies on the causal relationships between plant-derived foods and cancer risk by location. The results are classified as strong evidence, sub-divided into convincing (evidence is strong enough to justify dietary recommendations; and is robust enough to be highly unlikely to be modified) and probable (evidence is strong enough to support a causal relationship which generally justifies dietary recommendations), and limited-suggestive, when it is inadequate to support a probable or convincing causal relationship, but is suggestive of a direction of effect (see Unit 1.1).

Table 1. Plant foods and the risk of cancer, evidence from the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR)

Food exposure	Cancer Site	↑ or ↓ risk	Evidence
Strong evidence			
Wholegrains	Colorectum	↓	Probable
Fruis and vegetables	Aerodigestive tumors*	↓	Probable
Preserved vegetables by salting	Stomach	↑	Probable
Limited evidence			
Vegetables	Mouth	↓	Suggestive
	Pharynx	↓	Suggestive
	Larynx	↓	Suggestive
	Nasopharynx	↓	Suggestive
	Oesophagus	↓	Suggestive
	Lung	↓	Suggestive
	Breast	↓	Suggestive
	Bladder	↓	Suggestive
	Colorectum	↓	Suggestive
Fruits	Oesophagus	↓	Suggestive
	Lung	↓	Suggestive
	Bladder	↓	Suggestive
	Stomach	↓	Suggestive
	Colorectum	↓	Suggestive

**Includes mouth, pharynx and larynx, nasopharynx, oesophagus (squamous cell carcinoma and adenocarcinoma), lung, stomach and colorectal cancers*

Mechanisms of action

The mechanisms of action of plant-derived foods to decrease or increase carcinogenesis are normally due to the combined effect of several protective compounds, such as fiber, vitamins, minerals, and phytochemicals (especially polyphenols), although they may contain also harmful compounds (i.e. aflatoxins and acrylamide)

To find out more...

More information in Module 2.

Wholegrains

There is **strong** evidence that high diets in wholegrains **probably protects** against colorectal cancer.

Fruits and vegetables

There is **strong** evidence that greater consumption of fruits and vegetables combined **probably protects** against a number of aerodigestive cancers (including mouth, pharynx and larynx, nasopharynx, esophagus -squamous cell carcinoma and adenocarcinoma-), lung, stomach and colorectal cancers.

Vegetables (non-starchy vegetables)

There is **limited-suggestive** evidence that diets rich in vegetables are associated with a lower risk of cancers of the mouth, pharynx, larynx, nasopharynx, oesophagus (adenocarcinoma and squamous cell carcinoma), lung (particularly current and former smokers because they need more antioxidants to counteract the effects of tobacco), breast (only in estrogen receptor negative tumors), and bladder. A low intake of vegetables may be associated with a higher risk of colorectal cancer (limited-suggestive evidence).

High consumption of preserved vegetables (typically salt-preserved) is probably associated with a higher risk of gastric (strong evidence) and nasopharynx cancers (limited-suggestive evidence). This is the traditional way to preserve vegetables and fish in East Asia.

Fruits

There is limited-suggestive evidence that diets richer in vegetables are associated with a lower risk of cancers of the oesophagus (only squamous cell carcinoma), lung (particularly current and former smokers because they need more antioxidants to counteract the effects of tobacco), bladder and stomach (particularly with citrus fruit). A low intake of vegetables is associated with a higher risk of gastric and colorectal cancer.

Foods from animal origin

Major groups of foods from animal origin

Animal food is a term used to describe all foods of animal origin. These foods may be derived from the animal flesh itself (e.g., meat, fish, and poultry) or foods that are produced by animals (e.g., eggs, dairy products).

Animal foods are a good source of proteins of high biologic value, and some minerals (iron, zinc, selenium) and vitamins (vitamin B6, B12, D). Dairy products are also a rich source of calcium. The content and type of fat vary according the animal species, and rearing, processing and preserving methods. Animal fat is generally characterized as saturated and high in cholesterol.

Meat

Meat includes all animal flesh, either from the skeletal muscles or the internal organs (offal, such as the brain, liver, heart, intestines, and tongue). Meat can be further classed as either red meat, which generally refers to flesh from mammals that have more red than white muscle fibers (beef, veal, horse, goat, lamb, and pork), or white meat, which usually has more white than red muscle fibers: poultry (chicken and turkey) and rabbit.

¿Did you know...

Red meat is richer in fat, saturated fatty acids and cholesterol than white meat.

Meat contains between 11-23% proteins and can be a good source of iron, zinc, vitamin B12 and B6.

Iron is an essential micronutrient, which in mammals is generally found as haem iron in myoglobin, haemoglobin and cytochromes. Humans absorb about 15-35% of haem iron consumed; while only 2-5% of non-haem iron (mostly found in plants) is absorbed, although it can reach 20% in the presence of vitaminC.

Iron is notably required for oxygen transport as a component of haemoglobin, DNA synthesis as a component of ribonucleotide reductase, and as an electron acceptor/donor in the cytochromes that are essential for energy transduction.

However, haem iron has a catalytic effect on:

- the endogenous formation of carcinogenic N-nitroso compounds (nitrosamines) and
- the formation of cytotoxic and genotoxic aldehydes through lipoperoxidation.

¿Did you know...

If meat is cooked over an open flame, at high temperatures (grilled and barbecued), and charred or 'well-done', heterocyclic amines or polycyclic aromatic hydrocarbons can be formed.

To find out more...

Processed meat refers to meat that has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavour and increase, especially in the past, shelf-life. Processed meat usually refers to pork, but also beef, poultry, offal and meat by-products, such as blood. Processed meat products include bacon, ham, sausages, salami, corned beef, chicken nuggets, canned meat and meat-based sauces.

Minced meats, such as hamburgers or fresh sausages, are generally classified as processed meats.

A typical additive added to processed meats is nitrite, which is used as a bactericide and to give cured meats their color and flavour. Nitrite and nitrate can react with the degradation products of amino acids to form carcinogenic N-nitroso compounds (nitrosamines) during the curing process or in the human body (stomach). In most sausages, ascorbic acid and tocopherol (antioxidants) are added to partially inhibit the formation of nitrosamines.

Fish

Fish, or seafood, is any form of sea life used as food by humans. Seafood prominently includes fish and shellfish. Fish can be classified as marine-water (sardines or cod) and freshwater (trout or perch).

In nutrition, fish is usually classified according its fat content

Fish		Shellfish			
Lean fish (< 5% fat)	**Fatty fish (> 5% fat)**	**Molluscs**		**Crustaceans**	**Echinoderms**
		Bivalves	**Cephalopods**		
Cod	Sardines	Clams	Squid	Prawns	Sea urchins
Sole	Anchovies	Oysters	Octopus	Lobsters	Sea cucumbers
Hake	Salmon	Mussels	Cuttlefish	Crabs	
	Tuna				

Fish contains about 6-25% protein, and its fat content varies from less than 5% in lean fish and shellfish to 20% in some fatty fishes. Fish is also rich in vitamins (vitamin D, retinol, and B vitamins) and minerals (calcium, phosphorus, iron, zinc, iodine, magnesium, and potassium).

Fat from fish contains lower levels of saturated fatty acids than meat. Furthermore, fat from fish is generally rich in polyunsaturated n-3 fatty acids, eicosapentaenoic acid (EPA, C20:5 -3) and docosohexaenoic acid (DHA, C22:6 -3), which are long-chain fatty acids with several double bonds. The ability to make the longer-chain -3 fatty acids from -linolenic acid (C18:3 -3) may be impaired with aging. The -3 fatty acids may be beneficial in a wide range of diseases: cancer, asthma, depression, cardiovascular disease, and autoimmune diseases, such as rheumatoid arthritis. All these diseases have a common genesis in inflammation, and -3 fatty acids made eicosanoids that are often referred to as anti-inflammatory.

Fish and shellfish have the potential to absorb pollutants that are washed into rivers and oceans, most of which are lipophilic and tend to accumulate in their fat. Species of fish that have longer lifespans and that are high on the food chain, such as tuna, shark and swordfish, contain higher concentrations of pollutants than others. These pollutants can include heavy metals (mercury, lead) and the industrial compounds polychlorinated biphenyls (PCB).

¿Did you know...

Grilled and barbecued fish can also form polycyclic aromatic hydrocarbons.

To find out more...

The most common preserving method for fresh fish is salting. Depending on the specific conditions, salt-preserved fish may also undergo fermentation. The degree of fermentation that occurs depends on the freshness of the raw fish, the amount of salt used, the outdoor temperature, and the duration of the drying process. Cantonese-style salted fish is characterised by using less salt and a higher degree of fermentation during the drying process, because of the relatively high outdoor temperature and moisture levels. This leads to the formation of nitrosamines and nitrosamine precursors. It is a traditional part of the diet in southern China, Taiwan, Malaysia, and Singapore.

Dairy products

Dairy products include milk and milk products, such as yoghurt, cheese, butter and ghee.

Milk	**Yoghurt**	**Cheese**	**Butter and ghee**
Milk is produced by all mammalian species, although only milk produced by ruminants (cow, sheep, goat, and buffalo) is consumed by humans.	Yoghurt is produced through the bacterial fermentation of milk. Fermentation of lactose produces lactic acid, which acts on the milk protein to give yoghurt its texture and characteristic tart flavour.	Cheese is formed by coagulation of the milk protein, casein. Coagulation is due to acidification or the addition of the enzyme rennet.	Dairy fats include butter (80% fat content) and ghee, a type of clarified butter (99.5% fat content).

Whole dairy products have a high proportion of energy from fat, mainly saturated fat, and protein, and are rich in certain vitamins (retinol, vitamin D, vitamin B2 and B12) and minerals, especially calcium and phosphorus.

Dairy products are generally good sources of calcium, which is involved in a variety of functions in the body, such as bone metabolism, nerve and muscle activity, and the control of cell differentiation and proliferation.

¿Did you know...

Some cheeses can be consumed fresh; other types must undergo a ripening process under controlled conditions where different ingredients, particularly herbs and spices, can be added. Some cheeses have additional bacteria or moulds intentionally introduced before or during aging.

To find out more...

In countries where the consumption of dairy products is high, these are the main sources of calcium. Reduced-fat (semi-skimmed and skimmed) milks contain less fat and fat-soluble vitamins. Milk also contains the sugar lactose, which in lactose-intolerant people (common in Asian populations) leads to a decrease in the consumption of dairy products.

Eggs and animal fats

The most commonly consumed eggs are **chicken eggs**. Other poultry eggs include duck, quail and ostrich. Fish eggs (roe or caviar) and turtle eggs are not included here. The yolk is rich in fat, 27% of which is saturated, and cholesterol; whereas the white is rich in protein (13%).

Eggs are also a good source of vitamins (retinol, b vitamins, vitamin D) and minerals (potassium, zinc).

Animal fats are classified into animal fat or lard, and marine oils (fish and fish liver oils).

Animal fat is rich in saturated fatty acids and cholesterol, while marine oils are rich in polyunsaturated fatty acids, especially -3 (omega-3). Marine oils are usually very rich in fat-soluble vitamins (vitamin A and D).

Is there evidence of a relation between the type of animal food and the risk to suffer cancer?

Animal foods and the risk of cancer, evidence from the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR):

Food exposure	Cancer Site	↑ or ↓ risk	Evidence
Strong evidence			
Processed meat	Colorectum	↑	Convincing
Red meat	Colorectum	↑	Probable
Cantonese-style salted fish	Nasopharynx	↑	Probable
Dairy products	Colorectum	↓	Probable
Limited evidence			
Red meat	Nasopharynx	↑	Suggestive
	Lung	↑	Suggestive
	Pancreas	↑	Suggestive
Processed meat	Nasopharynx	↑	Suggestive
	Oesophagus	↑	Suggestive
	Lung	↑	Suggestive
	Stomach	↑	Suggestive
	Pancreas	↑	Suggestive
Fish	Liver	↓	Suggestive
	Colorectum	↓	Suggestive
Barbecued fish and meat	Stomach	↑	Suggestive

Dairy products	Breast	↓	Suggestive
	Prostate	↑	Suggestive

The imputed mechanisms of action of meat, processed meats and barbecued meat to increase carcinogenesis are related to the generation of potentially carcinogenic N-nitroso compounds (nitrosamines) in the stomach, or in gut by the gut bacteria. Some red meats are cooked at high temperatures resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons.

Haem iron promotes the formation of N-nitroso compounds but it can also lead to the production of free radicals.

Cantonese-style salted fish contains nitrosamines and nitrosamine precursors. Protective mechanisms of action of the consumption of fish against cancer are mainly related to -3 polyunsaturated fatty acids. Alternative suggestions include the relatively high selenium or vitamin D content of fish.

The potential effect of dairy products in reducing cancer risk is likely to be mediated at least in part by calcium; as intracellular calcium directly influences cell growth and apoptosis.

Evidence for animal-derived foods in relation to cancer

Red meat

There is **strong** evidence that consumption of red meat **probably** causes colorectal cancer. There is limited-suggestive evidence that consumption of red meat increases the risk of the following types of cancers: nasopharynx, lung and pancreas. The evidence suggesting that consumption of grilled and barbecued meat increases the risk of gastric cancer is limited.

Processed meat

The consumption of processed meat is a **convincing cause** of colorectal cancer. It has been estimated that the risk increases by 18% for each 50 grams/day of processed meat consumed. There is limited-suggestive evidence that eating red meat increases the risk of the following types of cancers: nasopharynx, oesophagus (only squamous cell carcinoma) lung, stomach (only non-cardias) and pancreas

Fish

There is **probable** evidence that consumption of Cantonese-style salted fish is **probably a cause** of nasopharyngeal cancer. Moreover, the intake of grilled and barbecued fish is suggested to increase the risk of stomach cancer. On the other hand, the consumption of fish may decrease the risk of liver and colorectal cancer (limited-suggestive evidence).

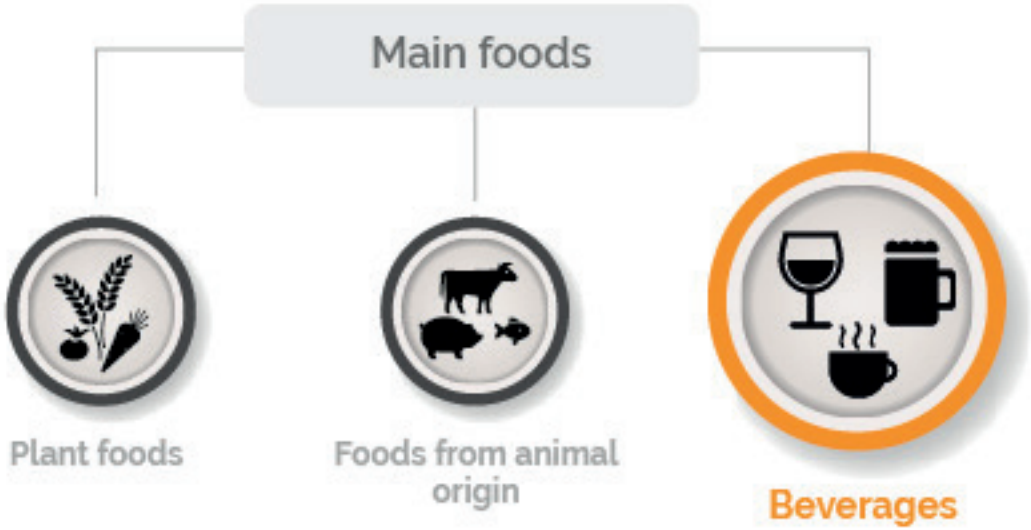
Dairy products

There is **strong** evidence that diets high in dairy products **probably protect** against colorectal cancer. There is limited-suggestive evidence that diets high in dairy products and calcium are associated with a lower breast cancer risk. However, diets rich in dairy products and calcium are associated with a higher prostate cancer risk.

Beverages

Major groups of beverages

Beverages, or drinks, are liquids for human consumption. In addition to their basic function of hydration, drinks play an important role in human culture. There are two main classes with very different properties: non-alcoholic and alcoholic beverages.



Non-alcoholic beverages

- Water

  Drinking water includes tap and bottled water. The water content of our body is around 70%; and approximately 80% of water intake comes from drinks and 20% from foods. Water can come from rain, springs, freshwater lakes, rivers, reservoirs and aquifers accessed by wells. Drinking water can contribute to the intake of minerals (calcium, iron, copper), depending on its origin and the piping materials used. It can also provide fluoride, either naturally or through fluoridation. Drinking water quality is regulated in most countries based on World Health Organization guidelines, although access to clean water is limited in many developing countries, especially for the poorest segments of these populations and those living in rural areas, who are at risk of exposure to water-borne diseases (cholera, dysentery, diarrhoea, schistosomiasis) and contaminants (arsenic). Drinking water can be contaminated with arsenic due to mining and industrial practices, but it can also be present naturally because of natural geological deposits or volcanic activity. Inorganic arsenic (arsenate or arsenite) is the predominant form in drinking water.

- Hot drinks

  Hot drinks are generally infusions brewed with boiling water, which are usually drunk when warm or hot. This group includes coffee, tea, mate, and herbal tea. Tea and coffee are the most consumed beverages after water.

  Coffee is a brewed drink prepared from roasted coffee beans. There are several methods of preparing coffee: boiled, infused, filtered, percolated, vaporised under pressure (espresso) or dissolved in water in the form of instant coffee. Instant coffee comprises the soluble solids derived from dried, double-brewed coffee. Decaffeinated coffees are produced through various processes, using water, organic solvents, steam, or by interfering with the expression of the gene coding for caffeine.

  Tea is a brewed drink prepared by pouring boiling water over dried leaves of the plant Camelia sinensis. The most commonly consumed teas are green tea in East Asia and black tea in Europe and West Asia. Green tea is made from tea leaves that are simply steamed and dried soon after harvest. Black tea is made from tea leaves that are dried, crushed and fermented to convert some of the simple flavonoids (catechins) into more complex forms known as theaflavins and thearubigins. These compounds are responsible for the distinctive flavour and darker color of black tea.

  Mate is an herbal tea, prepared from the dried leaves of the plant Ilex paraguariensis. Mate is generally drunk when very hot (above 65ºC). Other herbal teas, less commonly called tisanes, include infusions or decoction of herbs, spices, or other plant material in hot water, such as chamomile, peppermint, ginseng, etc.

  All hot drinks are good sources of polyphenols that have shown anti-cancer properties in cellular and experimental animal studies. In Europe, coffee and tea are the major sources of phenolic acids and flavonoids, respectively, and are also the main contributors to total polyphenols. Coffee, tea and mate also contain methylxantines, including caffeine, theophylline and theobromine. Caffeine is bioactive and improves reaction time, wakefulness, concentration, and motor coordination.

- Juices

  Juice is a drink made from the extraction or pressing of the natural liquid contained in fruit (oranges, pineapples, peaches, etc.) and vegetables (tomatoes). They can be fresh or commercial, which are generally pasteurised to extend their

shelf-live. Sometimes, **commercial juices** are concentrated at source and reconstituted before packaging, closer to the point of sale. In most developed countries, the term "fruit juice" can only legally be used to describe a 100% fruit juice (including those reconstituted from concentrate). Fruit juices may also contain some additives such as vitamin C. **Nectars** are fruit drinks that contain between 25-50% fruit juice, plus sugar, water and additives. A **smoothie** is a thick, cold beverage made from pureed raw fruit and/or vegetables, typically using a blender. Smoothies are often blended with other ingredients such as water, crushed ice, fruit juice, sweeteners (e.g. honey, sugar, stevia, syrup), dairy products (e.g. milk, yogurt), plant milk, nuts, seeds, chocolate, or herbs and spices. Fruit and vegetable juices have different nutritional properties from whole fruits and vegetables. They are rich in sugar and have low fiber content. In some cases, they are good sources of vitamin C, folate and potassium. Owing to these reasons, the international 'five-a-day' campaign to encourage people to eat more fruits and vegetables recommends that juices only count as one portion per day, irrespective of the amount consumed. One portion of fruit or vegetable juice is equal to 150mL.

- Soft drinks

  A soft drink is a drink made from water or carbonated water, a sweetener (sugar or an artificial sweetener in diet drinks), and natural or artificial flavourings (e.g. fruit juice, cola). Soft drinks are called "soft" in contrast to "hard" alcoholic drinks. Sports drinks are beverages whose stated purpose is to help athletes replace water, electrolytes, and energy before and after training or competition. Therefore, they contain sugars, electrolytes, and other additives. An energy drink is a type of drink containing stimulant compounds, usually including caffeine, which is marketed as providing mental and physical stimulation. These may or may not be carbonated and many also contain sugar or other sweeteners, herbal extracts, taurine, and amino acids.

Alcoholic beverages

An alcoholic beverage is a drink that contains ethanol, a type of alcohol produced through the fermentation of grains, fruits, or other types of sugar.

Alcoholic drinks include beers, wines, ciders, and spirits. Alcohol has an energy content of 7 kilocalories per gram, and is metabolised in the liver. It alters the way the central nervous system functions. The short-term effects of alcohol are, in low concentrations, improved mood and a feeling of euphoria, and increased self-confidence and sociability; however, in high doses, alcohol causes confusion, blurred vision, impaired speech, dizziness, vomiting, and in very high doses, unconsciousness and death. The long-term effects of alcohol in moderate doses seem to be associated with decreased risk of cardiovascular diseases, type II diabetes and overall mortality; however, high doses increase cardiovascular diseases, liver cirrhosis, alcoholism and premature death.

¿Did you know...

There is no global consensus on the recommended maximum intake of alcohol worldwide. In several countries moderate daily alcohol consumption is considered 1-2 standard alcoholic drinks in women and 2-3 in men. One standard drink contains around 10 grams of alcohol (~125mL of wine, ~250mL of beer/cider, ~40mL of spirits). The American Heart Association recommends that those who do not already consume alcoholic beverages should not start doing so because of the negative long-term effects of alcohol consumption.

Beer is brewed from cereal grains, most commonly malted barley, although wheat, corn, and rice are also used. During the brewing process, fermentation of the starch sugars by yeasts produces ethanol and carbonation in the resulting beer. Beer is one of the oldest and most widely-consumed alcoholic drinks in the world. Its alcohol content ranges from around 3-7% volume. Beers generally contain a variety of polyphenolic compounds, which contribute to the taste and color, and minerals (magnesium, potassium), and vitamins (riboflavin, folate).

Wine is brewed from grapes fermented by yeast. The color and the strength of the wine are affected by the different grapes, soil, climate, and wine-making processes used. The main types of wine are red, white and rosé wine. Their alcohol content ranges from around 9-15% volume. Red wine is very rich in polyphenols because the vinification process involves the extraction of color and flavour components (mostly polyphenols) from the grape skin, which is the richest part of the grape. Other types of wines include sparkling wines (such as champagne, cava, and prosecco) that contain large amounts of carbon dioxide. Fortified wines (such as porto, sherry, and vermouth) are wines with higher alcohol content, between 16-20% volume, due to being fortified with spirits. Low-alcohol and alcohol-free wines are rarely available. Apart from alcohol and polyphenols, wine also contains small amounts of sugars, minerals (magnesium, potassium, calcium, copper and iron) and vitamins (vitamin B1, B2 and B6).

Cider is made from the juice of apples that has been fermented by yeast. Its alcohol content ranges from 3.5-12% volume; cider also contains sugar and small amounts of vitamin C and minerals (potassium).

Spirits, or liquors, are produced by distillation of fermented grains, fruit, or vegetables. Distilled drinks may have herbs and other ingredients added to give them their distinctive character. The most common spirits are brandy (distilled wine), whisky and gin (distilled from grains), rum (from sugarcane), vodka (from cereal grains or potatoes), and tequila and mescal (from agave and cactus plants). Spirits and liqueurs can also be made from fruit. Their usual alcohol content is between 35–50% volume. Some spirits may also contain small amounts of polyphenols.

Evidence for beverages in relation to cancer

Table 2 summarizes the findings from epidemiological and mechanistic studies on the causal or protective relationships between beverages and cancer risk by location.

Table 2. Beverages and the risk of cancer, evidence from the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR)

Food exposure	Cancer Site	↑ or ↓ risk	Evidence
Strong evidence			
Alcoholic beverages	Mouth	↑	Convincing
	Pharynx	↑	Convincing
	Larynx	↑	Convincing
	Oesophagus	↑	Convincing
	Liver	↑	Convincing
	Colorectum	↑	Convincing
Coffee	Liver	↓	Probable
	Endometrium	↓	Probable
Mate (very hot drinks)	Oesophagus	↑	Probable

Alcoholic beverages	Breast	↑	Probable
	Stomach	↑	Probable
	Kidney	↓	Probable
Limited evidence			
Coffee	Mouth	↓	Suggestive
	Pharynx	↓	Suggestive
	Larynx	↓	Suggestive
	Skin	↓	Suggestive
Tea	Bladder	↓	Suggestive
Mate (very hot drinks)	Mouth	↑	Suggestive
	Pharynx	↑	Suggestive
	Larynx	↑	Suggestive
Alcoholic beverages	Lung	↑	Suggestive
	Pancreas	↑	Suggestive
	Skin	↑	Suggestive

Mechanisms of action of non-alcoholic beverages (including coffee) to decrease carcinogenesis are normally due to their phytochemical content (polyphenols). The mechanism of action of very hot drinks to increase carcinogenesis seems to be the beverage temperature, but not to the composition of the beverage, as it causes thermal burns/injuries to the aerodigestive tract. Consumption of soft drinks, including sugar-sweetened beverages, is not directly related to cancer risk, but is directly associated with weight gain, obesity and type II diabetes, which are main risk factors for several types of cancer.

The mechanism by which alcoholic beverages increase carcinogenesis is assumed to be their alcohol content. The biological pathways by which alcohol have a carcinogenic effect are not fully understood, but the main mechanism is likely to include a genotoxic effect of acetaldehyde; other pathways include the induction of cytochrome P450 and associated oxidative stress, increased estrogen concentration, changes in folate metabolism, changes in DNA repair, and a role as a solvent for tobacco carcinogens.

- Coffee
  There is strong evidence that greater consumption of coffee probably protects against both liver and endometrium cancers. There is limited-suggestive evidence that coffee intake is associated with a lower risk of cancers of the mouth, pharynx, larynx, skin (basal cell carcinoma in both sexes and malignant melanoma in women).

- Tea
  Evidence suggesting that consumption of tea reduces the risk of bladder cancer is limited.

- Mate
  Regular consumption of mate, drunk at very hot temperatures, as is traditional in South America, is probably a cause of oesophageal squamous cell carcinoma. Moreover, there is limited-suggestive evidence that mate intake, consumed while very hot, may be associated with mouth, pharynx and larynx cancer risks.

- Alcoholic beverages
  Consumption of alcoholic beverages is a convincing cause of the following cancers: cancer of the mouth, pharynx, larynx, oesophagus (especially squamous cell carcinoma), liver, colorectum and breast (in postmenopausal women). Moreover, it is probably a cause of stomach and breast cancer (in premenopausal women). The evidence suggesting that consumption of alcoholic drinks increases the risk of cancer of the lung, pancreas and skin (basal cell carcinoma and malignant melanoma) is limited. On the other hand, there is strong evidence that alcoholic beverages probably protect against kidney cancer.

For cancer prevention, the recommendation is to decrease alcohol consumption as much as possible, because there is no safe alcohol consumption threshold. The finding that drinking alcohol (less than two drinks per day) probably protects against kidney cancer is far outweighed by the increased risk for other cancers.

Other nutritional factors

Defining key concepts

Physical activity

Physical activity is defined as:

> *[...] any bodily movement produced by skeletal muscles that requires energy expenditure above the resting metabolic rate.*

Physical activity includes many actions that are undertaken in different daily-living domains that include vocation, transportation, household work and leisure time. Although physical activity is closely related to exercise and physical fitness, these concepts have different meanings.

When physical activity is planned, structured, repetitive and usually performed to improve or maintain physical fitness, the appropriate term is **exercise**. Whereas **physical fitness** refers to a set of attributes that people have or achieve.

Cardiorespiratory endurance, body composition and muscular strength are examples of health-related components of physical fitness.

In the context of epidemiology and health, **five components of physical activity (PA)** are usually considered:

1. **Type of physical activity**: aerobic (activity that increases oxygen uptake and improves cardiovascular function, e.g. running), muscle-strengthening (e.g. lifting weights) and stretching.
2. **Setting**: where the activity is performed (leisure-time, vocation, commuting, etc.).
3. **Duration**: total time per day or per week engaged in the activity.
4. **Frequency**: how often PA is undertaken over time (e.g. a day, week, month).
5. **Intensity**: how hard the person works to do the activity.

Frequency + Intensity + Duration = Total volume of physical activity

Physical activity intensity can be mainly categorized in three types:

Light intensity physical activity
Activity that does not cause a noticeable change in breathing rate.

An intensity that can be sustained for at least 60 minutes.

Examples: ironing, dusting, walking at a slow pace.

Moderate intensity physical activity
Activity that can be conducted whilst maintaining a conversation uninterrupted.

An intensity that may last between 30 and 60 minutes.

Examples: brisk walking, dancing, gardening.

Vigorous physical activity
Activity in which a conversation generally cannot be maintained uninterrupted.

An intensity that may last up to about 30 minutes (or high intensity physical activity when it generally cannot be sustained for longer than about 10 minutes).

Examples: fast cycling, carrying heavy loads, fast swimming.

To find out more...

In Metabolic equivalents and changes in heart rate

Physical activity intensity can be also expressed in metabolic equivalent of tasks (METs) or heart-rate parameters. A MET is a physiological measure that reflects the energy cost of physical activity taking into account the oxygen uptake relative to a person's resting metabolic rate (amount of energy required to keep the body functioning at rest). It is estimated that our basic metabolic rate consumes 1 MET; light-intensity physical activities require an energy expenditure of 1.5 – 3 METs, moderate-intensity physical activities 3 to 6 METs, while vigorous-intensity physical activities more than 6 METs. In terms of heat-rate parameters, for vigorous-intensity physical activity, a person's target heart rate should be 70 to 85% of his/her maximum heart rate (fastest rate at which the heart beats in one minute); 50 – 70% for moderate-intensity physical activities, and 57 – 63% for light-intensity physical activities.

Sedentary behavior and obesity

Sedentary behavior (SB) is distinct from physical inactivity, although they are often used interchangeably. Physical inactivity refers to not meeting physical activity recommendations (150 minutes of moderate-intensity aerobic physical activity throughout the week or 75 minutes of vigorous-intensity aerobic). In contrast, sedentary behavior refers to those waking activities characterized by an energy expenditure of ≤1.5 METs while in a sitting or reclining posture. Sedentary behaviors occur within different contexts of our daily-living, which can include sitting during commuting, at workplace and during leisure time.

Obesity (BMI 25-29.9) and overweight (BMI 30-39.9) are defined as an excess of body adiposity/fatness, and they often occur when the calories consumed from food and drinks are higher than the calories burned (from either excessive food intake or insufficient physical activity). Adipose tissue stores the energy in the form of fat (fatty acids, especially triglycerides). It is important to distinguish between visceral fat and subcutaneous fat. Visceral fat is found in the abdominal cavity, around the internal organs, while subcutaneous fat lies beneath the skin, around the muscles of the upper arm, buttocks, belly, hips and thighs. Visceral fat is more metabolically active than peripheral subcutaneous fat, thus it may entail higher health risks.

Measures

Measures of physical activity (PA) and sedentary behaviors (SB) in free-living conditions

PA and SB can be assessed through different techniques that can mainly be categorized into subjective (self-reported) and objective measures.

Subjective measures of physical activity and sedentary behaviors

Self-reported measures, which include self/interviewed administered questionnaires and activity diaries, are considered subjective measures as they measure a persons' ability to recall their behavior. Recall questionnaires (e.g. I**nternational Physical Activity Questionnaire**) are the most common form of assessing self-reported PA and SB because they can be implemented on a large scale, they are relatively inexpensive, do not alter the behavior under study and they provide additional information about the context/domain where the behavior takes place.

However, self-reported instruments have some limitations. Questionnaires are susceptible to random and systematic reporting errors as recalling behaviors that are sporadic or intermittent in nature may be challenging and they are exposed to social desirability bias.

Objective monitoring of physical activity and sedentary behaviors: Motion sensors

Objective monitors such as **pedometers** (step counter) and **accelerometers** offer greater validity and reliability compared to self-reported data as they can provide more accurate assessments. Accelerometers can be broadly classified into those that mainly provide an approximation of energy expenditure (e.g. Actigraph) or those that primarily aim to classify posture (e.g. activPAL).

Energy-expenditure based accelerometers measure body accelerations (e.g. ActiGraph GT3X, GENEA). Through proprietary algorithms, these accelerations are converted in activity counts occurring in a specific time interval, which is referred as an epoch. The analysis of these counts allows researchers to estimate parameters of physical activity such as frequency, duration and intensity.

Posture-based accelerometers (e.g. activpal) use accelerations and body inclinations to accurately capture body positions. This type of device has been currently considered the gold standard for measuring sedentary behaviors.

Measures of body composition and obesity

- Body mass index (BMI)

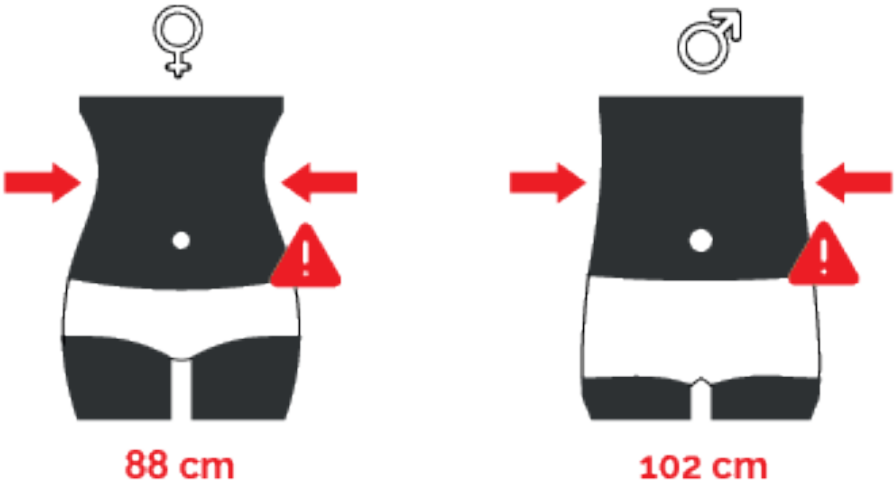
$$\text{Body mass index (BMI)} = \frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$$

The standard weight categories based on BMI for adults ≥20 years are:

BMI	Weight Category
18.5 – 24.9	Normal
25.0 – 29.9	Overweight
30.0 – 39.9	Obese
≥40.0	Severely obese

It should be noted that BMI does not differentiate between lean and adipose tissue mass, which is particularly important as lean (e.g. people that are very muscular) and adipose tissue mass have separate roles in determining cancer risk.

- Waist circumference



Waist circumference is a measure that assesses abdominal obesity. It is considered that there is abdominal obesity in adults when this circumference is greater than 102 cm in men and 88 cm in women.

Althought BMI and waist circumference are well validated measures and available to all health professionals, more complex and pricely methods are used in the research field (e.g. magnetic resonance imaging, dual X-ray absorptiometry and computerised tomography).

Summary of the evidence

Physical activity, sedentary behavior and cancer risk

It is well established that the more physically active people are, the lower risk of cancer. However, current evidence indicates that physical activity benefits are not homogenous for all types of cancers. In this section we will briefly analyze the preventive role of physical activity according to specific tumor locations.

Cancer risk	Current evidence
Colon cancer	There is **convincing evidence** that either total or leisure-time physical activity protects against colon cancer. Although the effects of physical activity on colon cancer risk are evident in both men and women, some studies indicate that the effects may be stronger in men. For rectal cancer, the evidence is still unclear. In regards to dose-response relationships, while there is not an established optimal dose of physical activity, research shows that the risk decreases with higher levels of physical activity.
Brest cancer	**Strong evidence** indicates that physical activity lowers the risk of breast cancers, with higher levels of physical activity producing higher protective effects. The evidence is clear for physical activity protective effect in postmenopausal breast cancer, while there is limited evidence for these effects on pre-menopausal breast cancers.
Endometrium cancer	There is **consistent** evidence showing that higher levels of physical activity either performed in occupational or recreational context, are related to a decreased risk of endometrial cancer. Similar to previous cancers, dose-response relationships are not yet determined.
Other tumors	For other tumors such as oesophagus, lung and liver the evidence for physical activity protective effects is weak and limited.

Physical activity and risk of cancer

	Decreases risk	Increases risk
Physical Activity	Colorectum (colon) (1)	
	Endometrium (1)	
	Breast (postmenopause) (1) (2)	
	Breast (premenopause) (2)	
	Oesophagus	
	Lung	
	Liver	
	Breast (premenopause)*	
Sedentary behaviors		Endometrium

Footnote: strong evidence-convincing; strong evidence-probable; limited-suggestive.

(1) The exposure of physical activity includes evidence for all types of activity and all intensity levels.

(2) In addition to physical activity, there was sufficient evidence to make a separate judgement for vigorous-intensity physical activity.

Source: modified from the *World Cancer Research Fund*/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective.* Continuous Update Project Expert Report 2018. Available at dietandcancerreport.org

To find out more...

Sedentary behaviors are ubiquitous in contemporary society, but the link between this lifestyle factor and risk of cancers has been less studied. Some evidence indicates that there could be a suggestive trend indicating an increased risk of endometrial cancer with higher levels of sedentary behavior. However, the evidence is still limited and robust conclusions cannot be drawn. Determining sedentary behavior's role in relation to cancer risk is a research priority.

Obesity and cancer risk

Obesity is currently considered a major public health challenge of the 21st century, affecting both low-income and high-income countries. This is a particularly important issue as obesity is associated with a higher incidence of a large number of diseases, including cancer.

Obesity and breast cancer	The effect of obesity on breast cancer goes in the opposite direction according to the menopausal status. In pre-menopausal women, obesity decreases the risk of breast cancer. This reduction is due to the fact that young obese women have a higher number of anovulatory cycles and lower levels of circulating steroid hormones (mainly progesterone and estradiol), which are one of the main causal factors of breast cancer. In post-menopausal women, obesity increases the risk of breast cancer. It is estimated that a BMI between 25 to 30 increases the risk by 30%, while a BMI equal to or greater than 30 increases the risk of breast cancer by 50%.
Obesity and colorectal cancer	Obesity is clearly associated with colorectal cancer. Obese people are approximately a 30% more likely to develop colorectal cancer than people with normal weight. A higher BMI is associated with higher risks of colon cancer and rectum in both men and women, but the risk is greater in men.
Obesity and pancreatic cancer	Strong evidence indicates that obesity increases risk of pancreatic cancer. The risk of pancreatic cancer is 1.3 times higher in people who are overweight and 1.7 times higher in people with obesity, compared to those who have a normal BMI. The risk seems to be similar in men and women.
Obesity and adenocarcinoma of the esophagus	There are two major types of esophageal cancers, according to the histology: the squamous type and the adenocarcinoma. There is convincing scientific evidence showing that obesity increases the risk of adenocarcinoma of the esophagus. Overweight and obese individuals have higher risk of adenocarcinoma of the esophagus compared to normal weight (2 and 3 times higher, respectively).

Obesity and endometrium cancer	There is also consistent epidemiological evidence indicating that a positive association between obesity and risk of endometrial cancer. Overweight and obese women are 2 to 4 times more likely than normal-weight women to develop endometrial cancer. It is important to highlight that the risk of endometrial cancer associated with obesity occurs in both pre and post-menopausal women.
Obesity and kidney cancer	Although kidney tumors are relatively rare, the most common is renal cell carcinoma. Strong evidence indicates that being overweight increases the risk of renal cell carcinoma by 1.5 times, while obesity increases the risk by 2.5 times compared to normal BMI. The evidence seems to indicate that there are no risk differences according to sex.
O**besity and liver cancer**	Compelling evidence indicated that overweight or obese people are up to twice as likely as people of normal weight to have liver cancer. The association between overweight and obesity and liver cancer is higher in men than in women.
Other tumors associated to obesity	Apart from the tumors already described, there is accumulating evidence indicating that the following tumors are associated to obesity: gall bladder, stomach (cardia), ovary, prostate, mouth, pharynx, larynx, thyroid, meningioma and multiple myeloma.

Body fatness and weight gain and the risk of cancer

	Decreases risk	Increases risk
Adult body fatness		Esophagus (adenocarcinoma) (1) Pancreas (1) Liver (2) Colorectum (1) Breast (postmenopause) (1) Endometrium (3) Kidney (1)
Adult body fatness	Breast (premenopause) (1)	Mouth, pharynx and larynx (1) Stomach (2) Gallbladder (2) Ovary (2) Prostate (advanced) (1)
Body fatness in young adulthood	Breast (premenopause) (4) Breast (postmenopause) (4)	

Footnote: strong evidence-convincing; strong evidence-probable.

(1) Conclusions for adult body fatness and cancers were based on evidence marked by body mass index (BMI), waist circumference and waist-hip ratio.

(2) Conclusions for adult body fatness and cancers were based on evidence marked by BMI.

(3) The conclusion for adult body fatness and endometrial cancer was based on evidence marked by BMI, weight gain, waist circumference and waist-hip ratio.

(4) Evidence for body fatness in young adulthood and breast cancer (pre and postmenopause) comes from women aged 18-30 years old and includes evidence marked by BMI.

Source: modified from the *World Cancer Research Fund*/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective.* Continuous Update Project Expert Report 2018. Available at dietandcancerreport.org

Brief overview of biological mechanisms linking physical activity, obesity and cancer

Based on the evidence from molecular epidemiological studies, several mechanisms have been suggested to explain the relationship between physical activity and cancer.

Physical activity has been shown to reduce cancer risk. Some of its benefits are:

- a healthy body weight,
- lower adiposity,

- reduction of insulin resistance,
- regulation of sex hormones,
- reduction of chronic inflammation and
- promotion of immune activity response.

In regards to obesity and body composition, there are several mechanisms by which obesity can increase the risk of cancer and they can vary depending on the cancer type.

Fat tissue produces excess amounts of estrogen.

Obesity increases blood levels of insulin and insulin-like growth factor-1.

Obesity also modifies the production of adipokines by fat cells.

Adiponectin increases insulin sensitivity and it may have an anti-inflammatory and protective effect against cancer.

Leptin is positively related to insulin resistance.

Lastly, fat tissue has an important inflammatory component (defined by the increased production of cytokines), which is a key factor for specific tumors.

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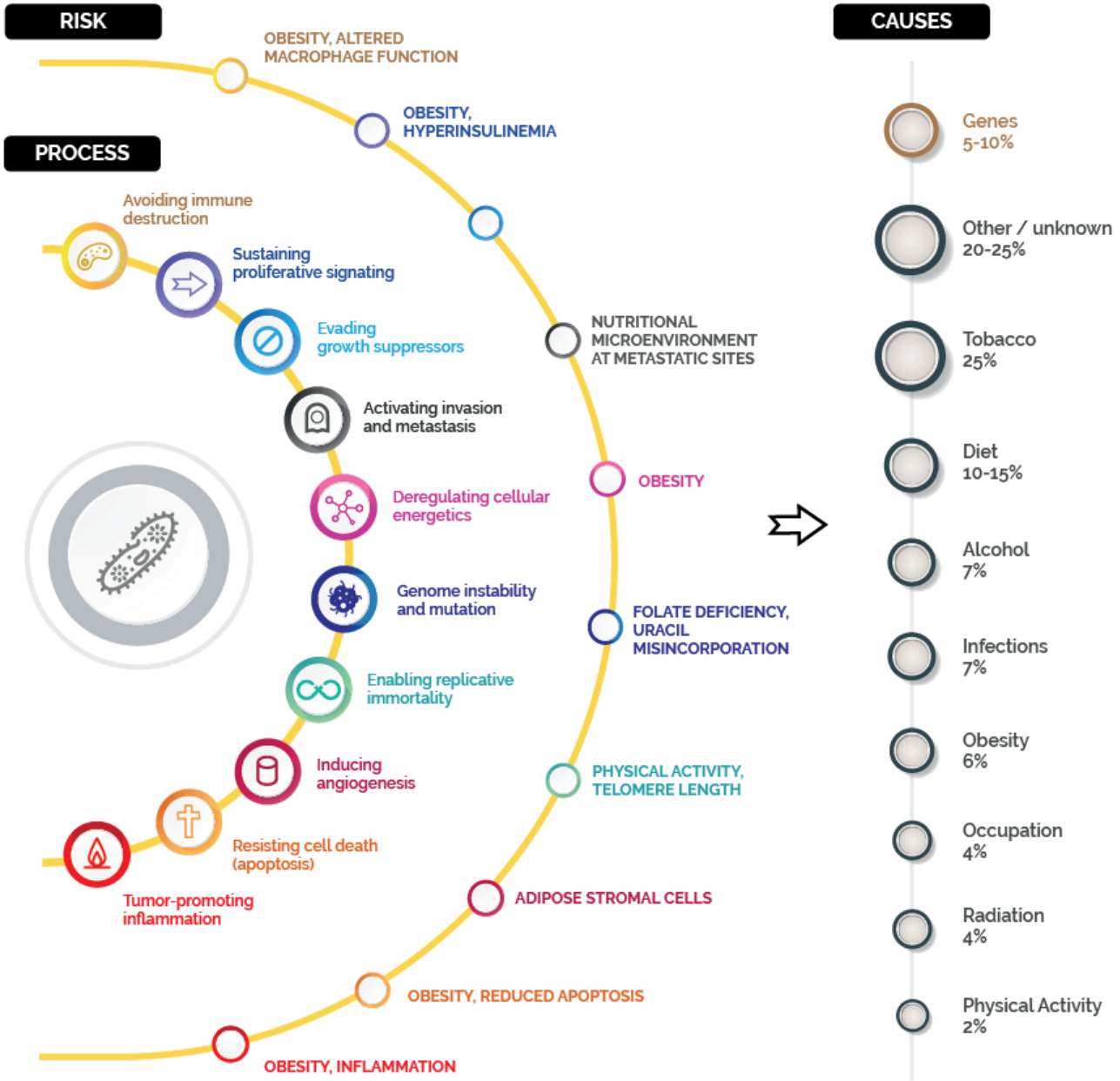

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Antonio Agudo is a physician with an expertise in epidemiology, preventive medicine and public health. He graduated in Medicine (MD) at the University of Barcelona and has a Master of Sciences in Clinical Epidemiology from the Erasmus University of Rotterdam. He completed his doctoral training at the Autonomous University of Barcelona, where he obtained a PhD in Public Health and Methodology of Biomedical Research.

Dr. Agudo started to work in cancer epidemiology by conducting case-control studies on lung cancer, mesothelioma, and head-and-neck cancer. He was involved in the design of and recruitment for the European Investigation into Cancer and Nutrition (EPIC) project, a large multicentric cohort study which was carried out in ten European countries. Since 1999, he is employed at the Catalan Institute of Oncology, where he currently holds a position as Head of the Unit of Nutrition and Cancer. He is also the coordinator of the EPIC cohort in Spain and the representative of EPIC-Spain at the EPIC Steering Committee, as well as a member of several other working groups of EPIC-Europe.

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Dr. Raul Zamora-Ros is graduated in both Nutrition and Food Science and also obtained a master on Statistics and Epidemiology. He earned his PhD in Nutrition from the University of Barcelona in 2008. He did his Post-Doc on Nutritional Epidemiology at the IDIBELL, International Agency for Research on Cancer (IARC) and the University of Cambridge, before joining his current position as principal investigator at the Unit of Nutrition and Cancer (IDIBELL) since February 2016. He is interested in whether dietary factors, particularly polyphenols and polyphenol-rich foods, are causally associated with the development of chronic diseases. He has published over 80 peer-review articles and above 10 book chapters in his area.

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