Evolutionary Medicine

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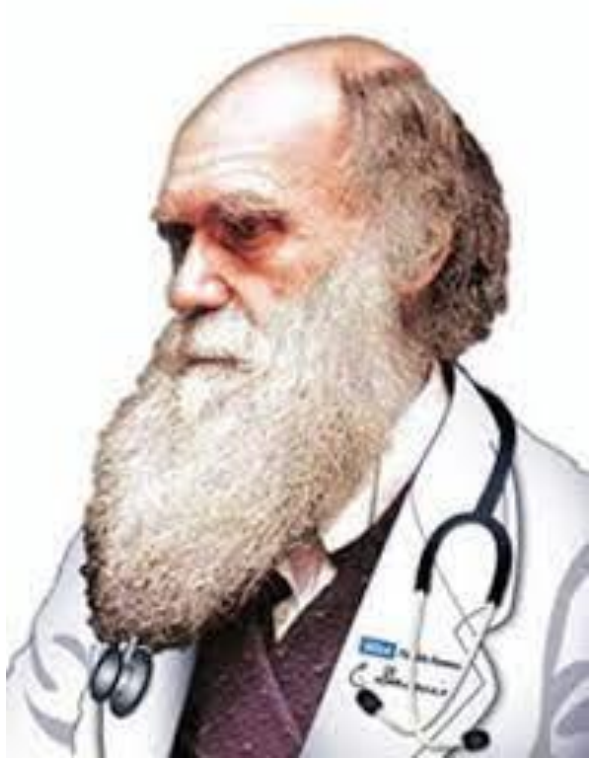

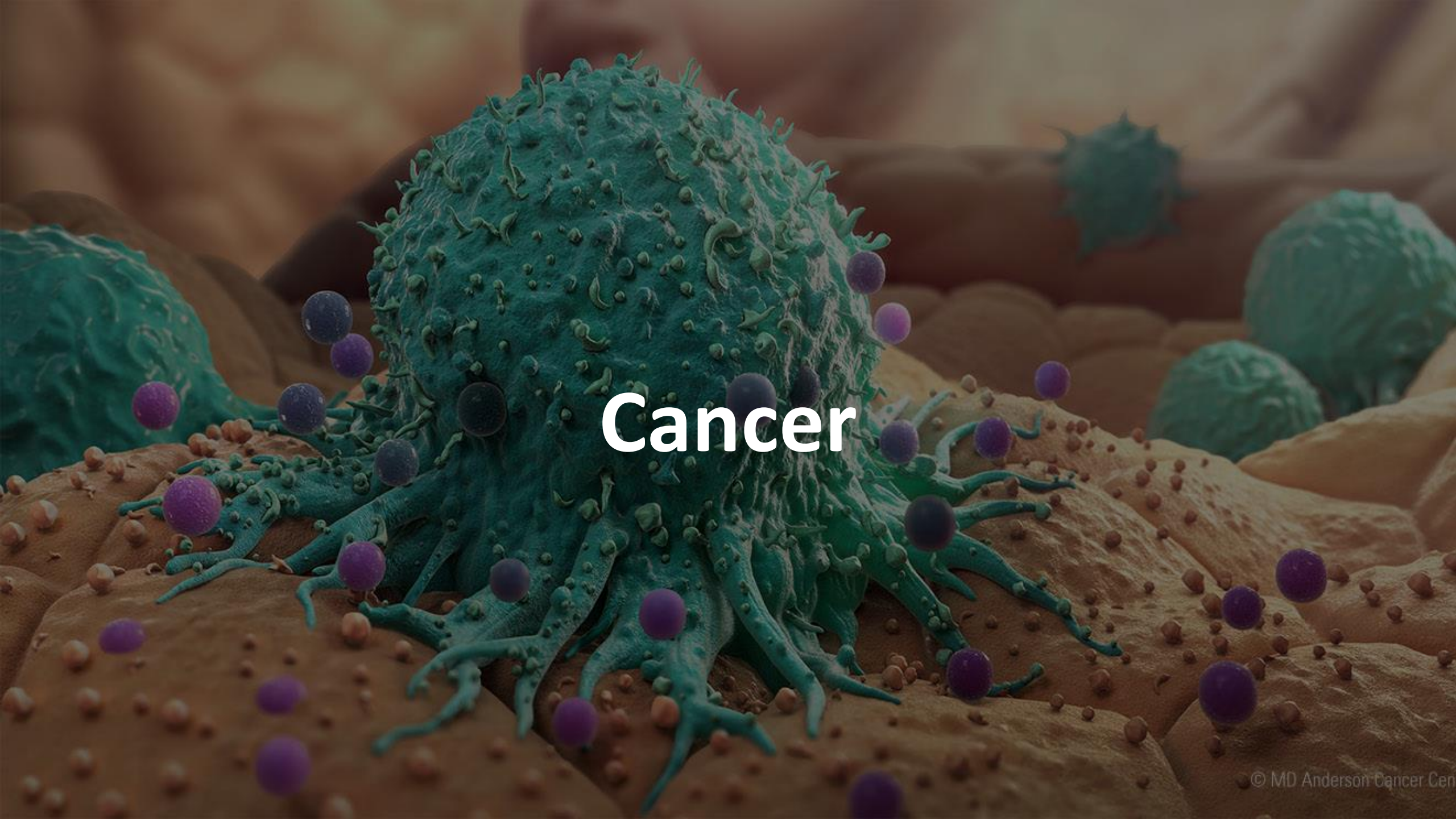
Cancer
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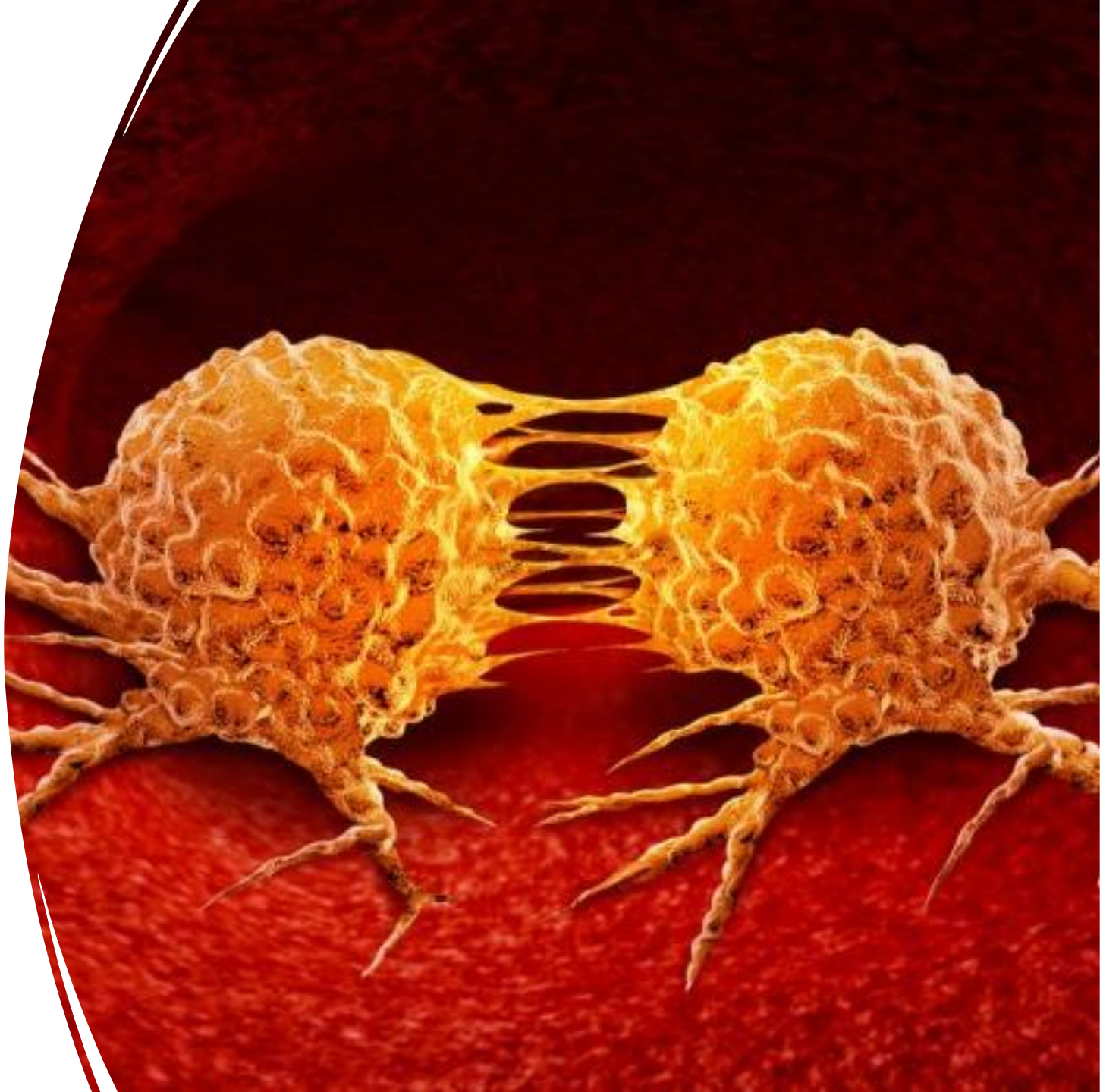
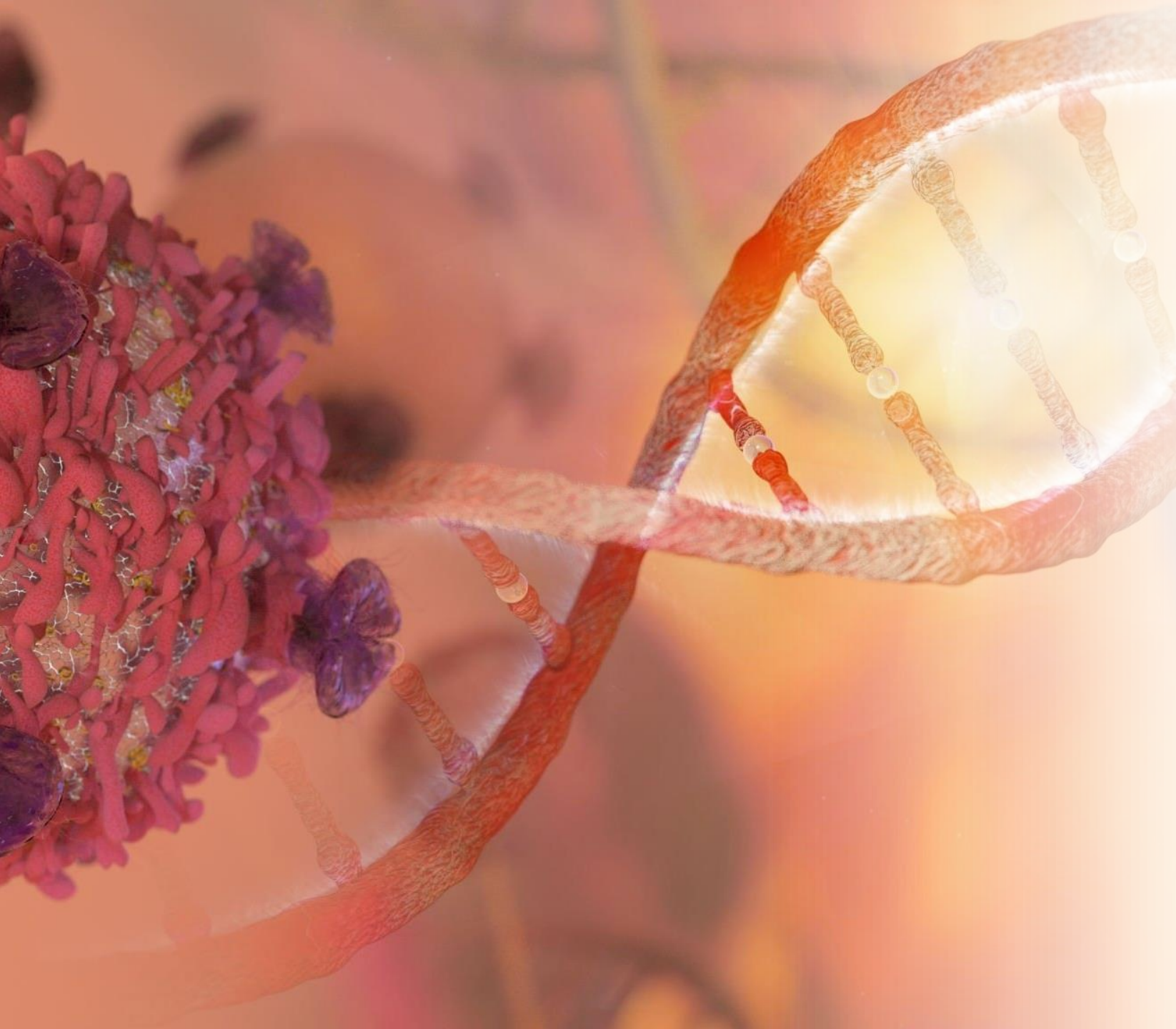
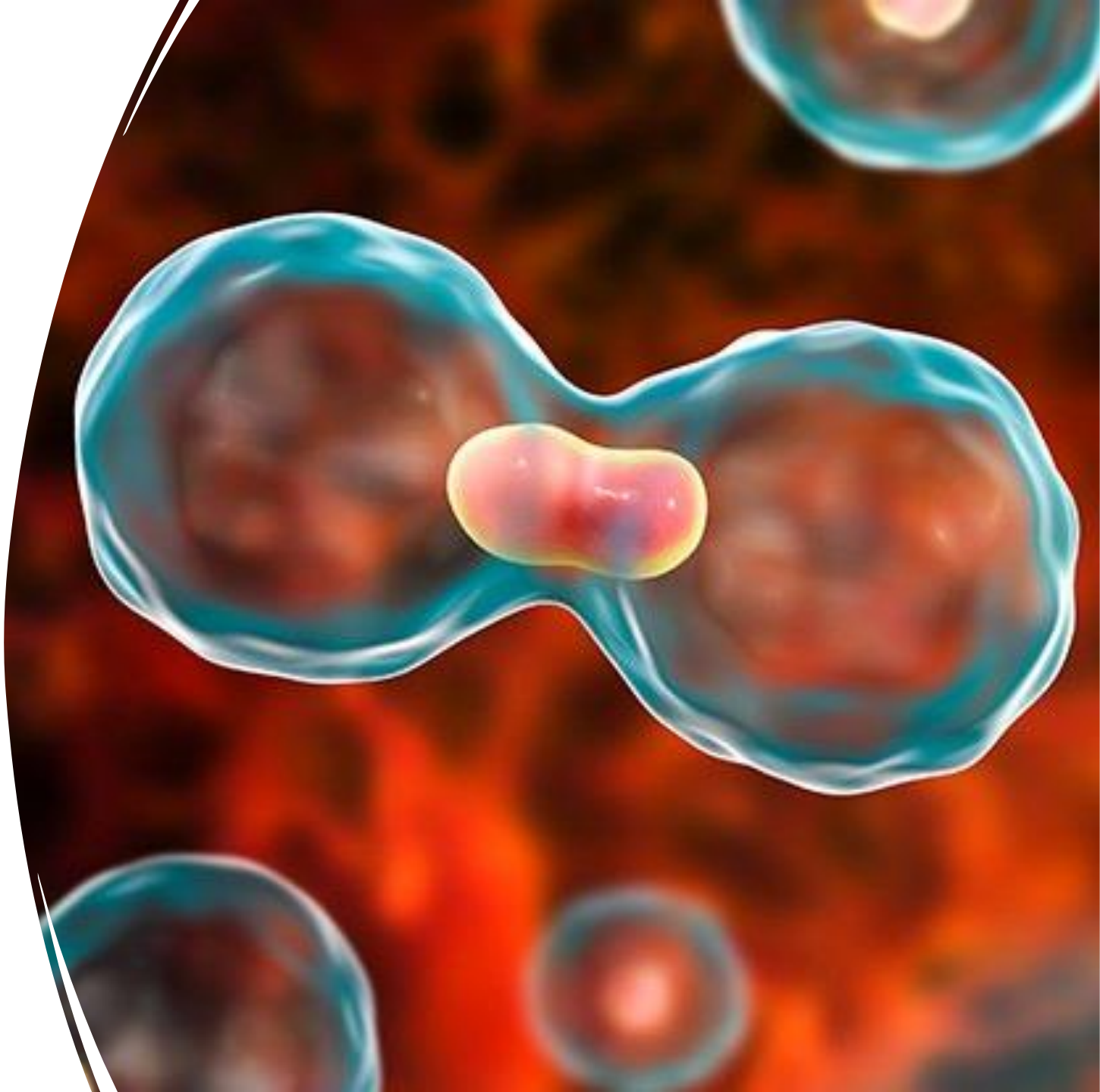
- Cancer is not a single disease entity: there are many pathways that can lead to uncontrolled replication of a cell population (carcinogenesis), the spread of a tumor into nearby tissue (invasion), and the migration of a tumor from the tissue where it originated to elsewhere in the body (metastasis). The complexities of the pathways leading to the apparently common phenomenon of uncontrollable cellular replication mean that while some specific and generally rare cancers can be traced to a singular initiating event, such as asbestos-induced mesothelioma, most cancers—even of a single type—do not have a single cause, and hence prevention and therapy are not straightforward.





In cancer, the cell can be seen as the unit of selection, and its clonal expansion can be interpreted as a situation in which one cell lineage is proliferating at a cost to other cells in its neighborhood (and often, eventually, to their “vehicle”, the body). The cancer cell lineage is distinguished by having the capacity to override the normal processes inhibiting its growth, and its cells are effectively selected for this advantage, thus replicating and developing autonomy. Given that multicellular organisms are evolved coalitions of cells, cancer can be seen as a form of atavism where unicellular interests again become dominant, and selection operates at the level of the cell. Thus the proximate cause of cancer can be envisaged as the somatic mutations induced in the clone that give a particular lineage of cells a replicative advantage. But evolutionary processes provide the ultimate cause in that these cells win the competition for selection. Cancer cells have particular abilities that make them more able to adapt to the selective pressures of the environment.

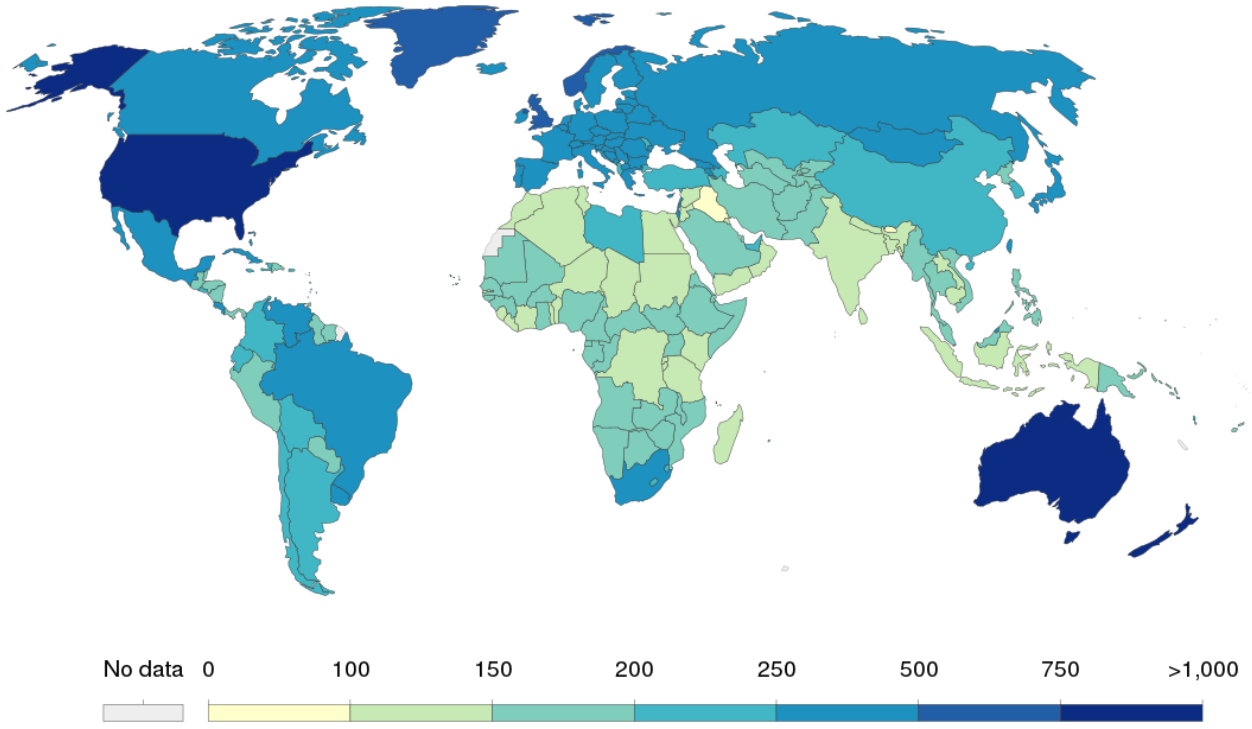
- Consider the very nature of a metazoan: its life history originates from a single pluripotent cell which ultimately differentiates into multiple cell types and forms organs with residual capacities for repair, which is in turn dependent on subpopulations of stem cells. It needs to organize and regulate its development, a process that frequently involves not only the promotion of cell growth and differentiation but also the regulation of apoptosis (programmed cell death). Mutational escape from each of these multiple layers of control is the primary proximate mechanism for the origin of malignancy. However, most cells that undergo a mutation that could develop into a malignancy do not survive the biological bottlenecks (tumor suppression mechanisms) that place limits on the ability of the cellular clone to grow and become autonomous. Nowell (1976) realized a generation ago that selective processes of somatic evolution operate within a tumor to generate sub-clones that vary phenotypically with respect to traits such as the capacity for growth or drug resistance, and that these evolutionary processes might best be countered by designing individualized therapies for patient and tumor characteristics. Recently we have come to understand that metastases undergo further mutations, and that each metastasis may have a different genetic profile from the primary tumor, thus leading to further therapeutic challenges and demonstrating successful (from the tumor's perspective) evolution.



Epidemiology of Cancer

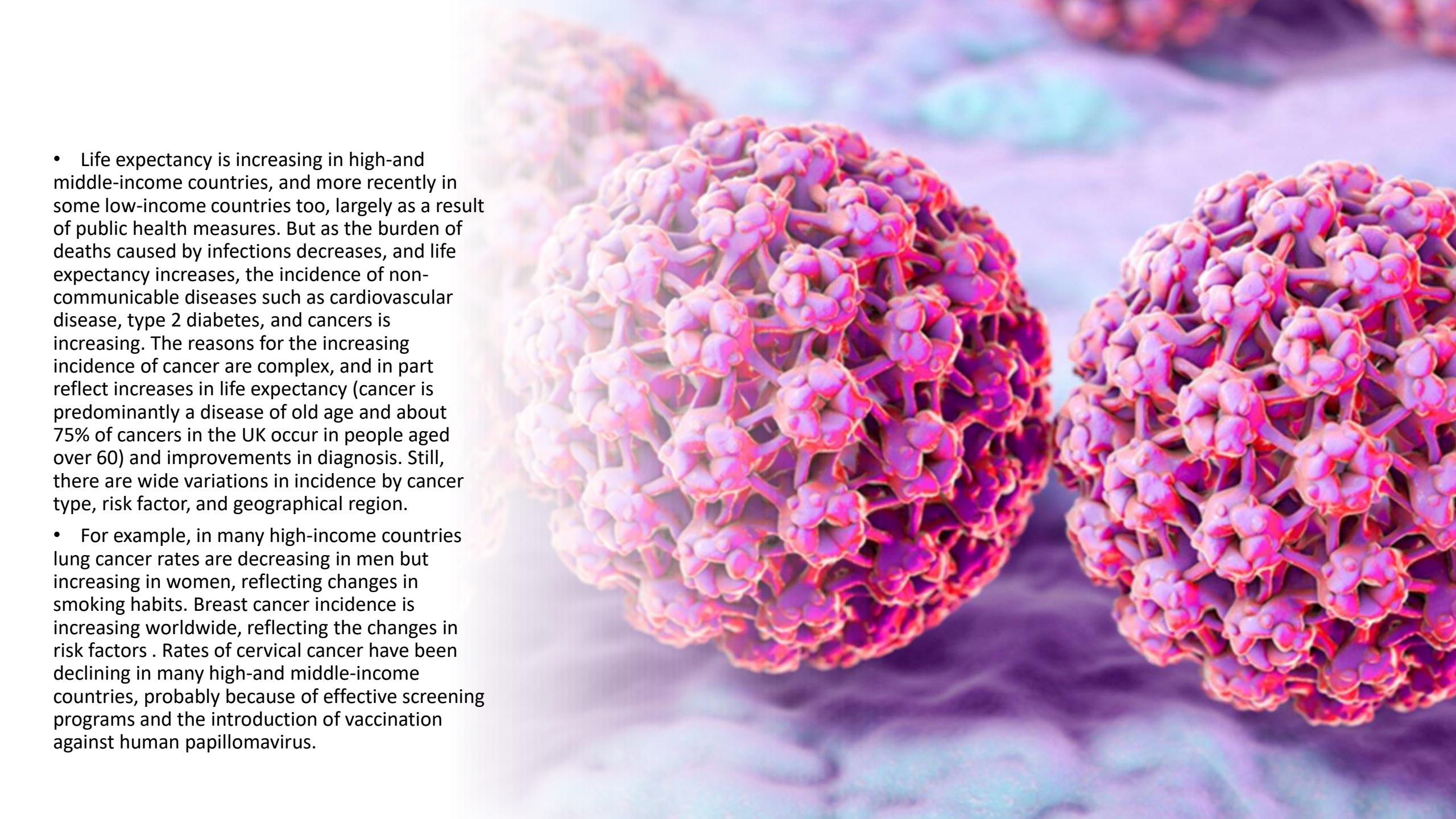
Cancer incidence, 2017

New cases of any type of cancer (i.e. incidence) measured as the number of new cases per 100,000 people. This has been age-standardized, assuming a constant age structure of the population for comparisons between countries and over time.

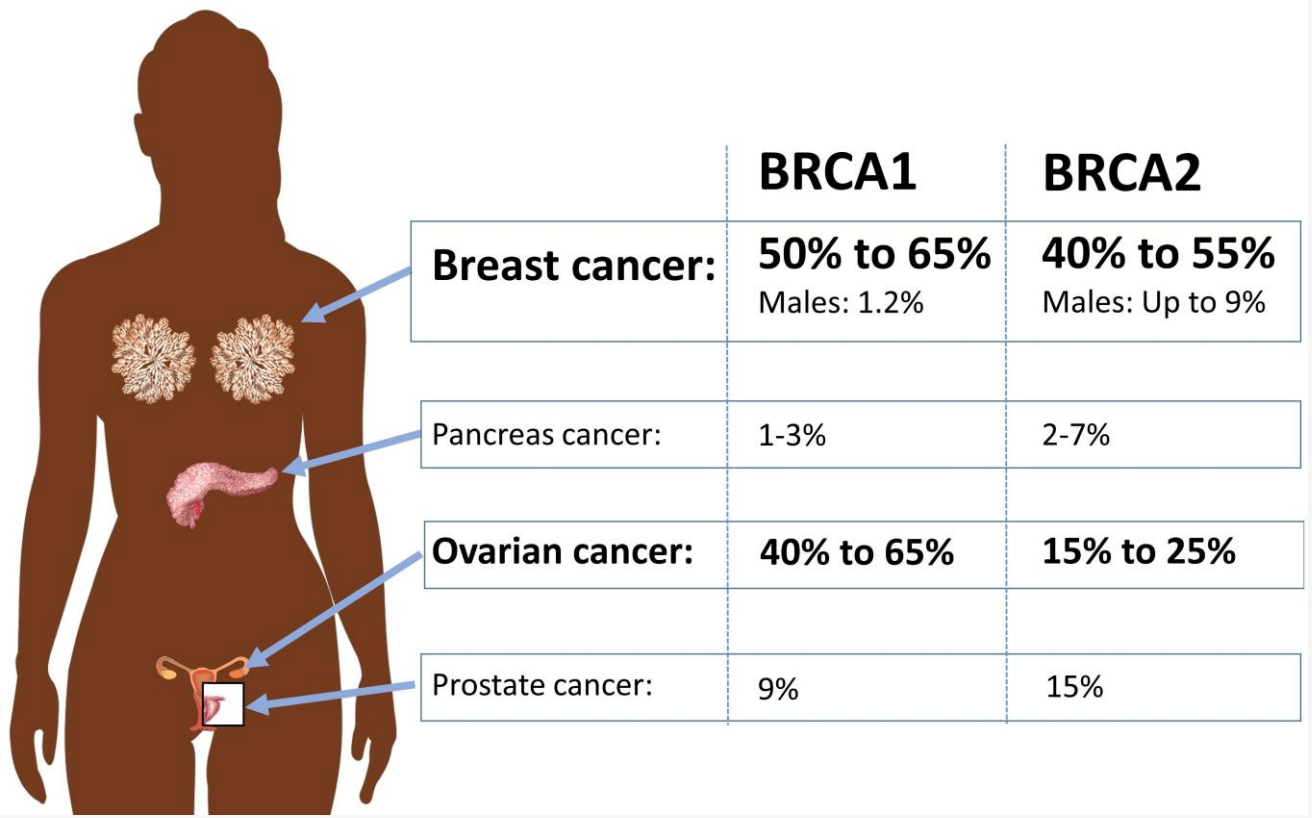


Source: Institute for Health Metrics and Evaluation (IHME)

- Life expectancy is increasing in high-and middle-income countries, and more recently in some low-income countries too, largely as a result of public health measures. But as the burden of deaths caused by infections decreases, and life expectancy increases, the incidence of non-communicable diseases such as cardiovascular disease, type 2 diabetes, and cancers is increasing. The reasons for the increasing incidence of cancer are complex, and in part reflect increases in life expectancy (cancer is predominantly a disease of old age and about 75% of cancers in the UK occur in people aged over 60) and improvements in diagnosis. Still, there are wide variations in incidence by cancer type, risk factor, and geographical region.
- For example, in many high-income countries lung cancer rates are decreasing in men but increasing in women, reflecting changes in smoking habits. Breast cancer incidence is increasing worldwide, reflecting the changes in risk factors . Rates of cervical cancer have been declining in many high-and middle-income countries, probably because of effective screening programs and the introduction of vaccination against human papillomavirus.



- Malignant disease will ultimately affect more than a quarter of the population of high-income countries. In 2012, cancer caused over 8 million deaths worldwide (15% of all deaths; more than AIDS, malaria, and tuberculosis combined). In high-income countries, cancer was the second most common cause of death, after cardiovascular disease. In low- and middle-income countries, the high mortality caused by infectious and parasitic diseases meant that cancer was the third most common cause of death. However, the high burden of infection in low-and middle-income countries means that nearly a quarter of newly diagnosed cancers in these countries are attributable to infections (stomach cancer being an example) while less than a tenth of cancers in high-income countries have an infective origin (American Cancer Society 2015)

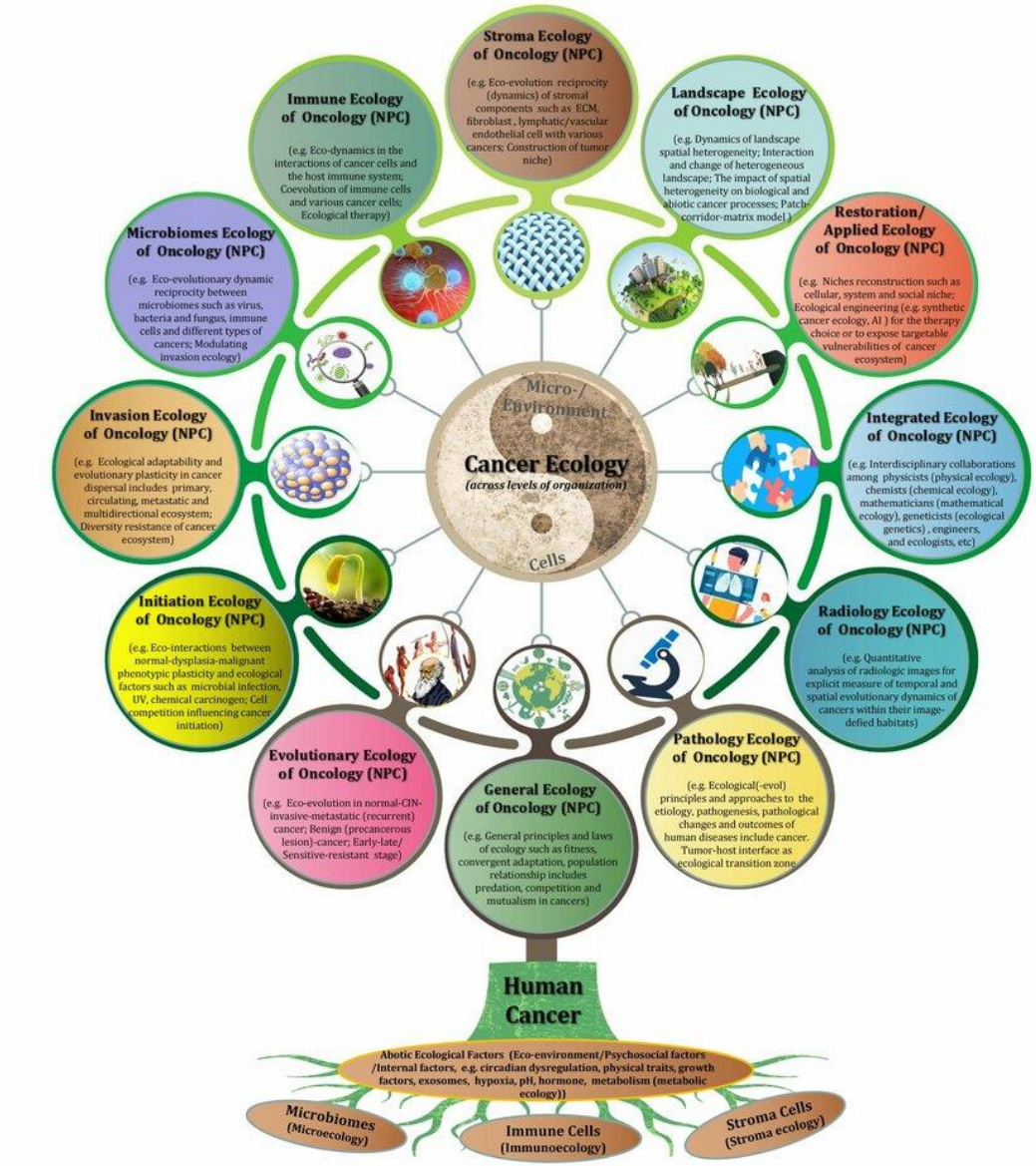


	BRCA1	BRCA2
Breast cancer:	**50% to 65%** Males: 1.2%	**40% to 55%** Males: Up to 9%
Pancreas cancer:	1-3%	2-7%
Ovarian cancer:	**40% to 65%**	**15% to 25%**
Prostate cancer:	9%	15%

- Incidence rates for particular neoplasms vary widely across the world. Rates for some cancers, for example melanoma or esophageal cancer, can vary by up to 200-fold depending on geographical location. In the gastrointestinal tract, colorectal cancer and stomach cancer show very different geographical distributions, with the former having its highest incidence in Europe and North America and the latter in Asia. Liver cancer has its highest incidence in Africa, largely explained by the high rates of infection with hepatitis B and C. The incidence of prostate cancer also varies widely , likely as a result of nutritional and life-history factors. Environmental rather than genetic factors play a large role in these distributions of cancer incidence, as can be demonstrated by studies of migration between areas of different risk. For example, compared with non- migrants, people from northern Europe who migrate to semi-tropical areas experience greater rates of melanoma, whereas individuals moving from high-risk to low-risk areas for stomach and liver cancer experience lower rates of these neoplasms (Vineis and Berwick 2006). For some neoplasms, diet contributes to disease risk, possibly via an effect on the gut microbiota (O'Keefe et al. 2015).. Nevertheless, some population groups are more frequent carriers of founder mutations affecting cancer risk, such as the *BRCA1/2* mutations associated with breast cancer found in Ashkenazi Jews.

- But although the increasing incidence of cancer has led some to suggest that cancer is just a disease of “modern lifestyles” this is not the case. Although most cancers occur in soft tissue and would not be well preserved in skeletal remains, evidence of cancer (bone metastases originating in soft tissue neoplasms, as well as primary tumors such as osteosarcoma) can be found in fossilized human bones, including an osteosarcoma in the “Kanam jaw” from an early *Homo* species dating from around 500,000 years ago. Early Egyptian writings contain descriptions of what can only be ulcerating tumors, and comment on their refractoriness to treatment. Nearly 2500 years ago, the Greek physician Hippocrates described tumors by using the Greek word for crab (*karkinos*), the origin of the word cancer, and his later compatriot Galen referred to tumors as *oncos* (swelling), providing our modernname for the discipline of onkology.

Ecology of Cancer



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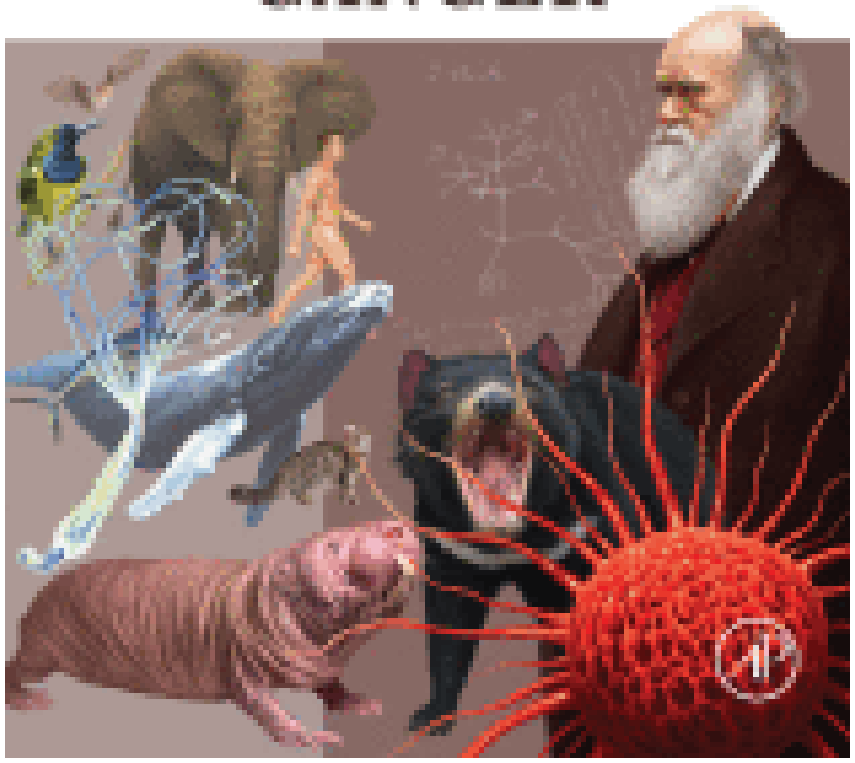
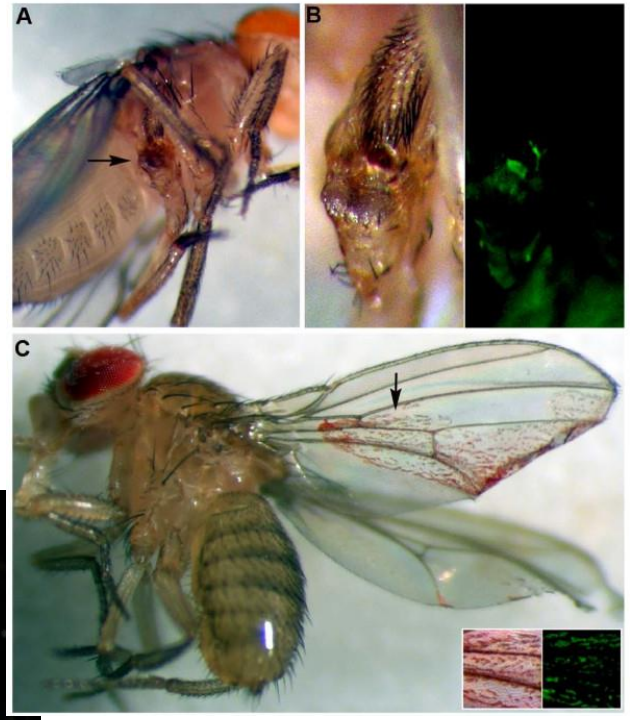
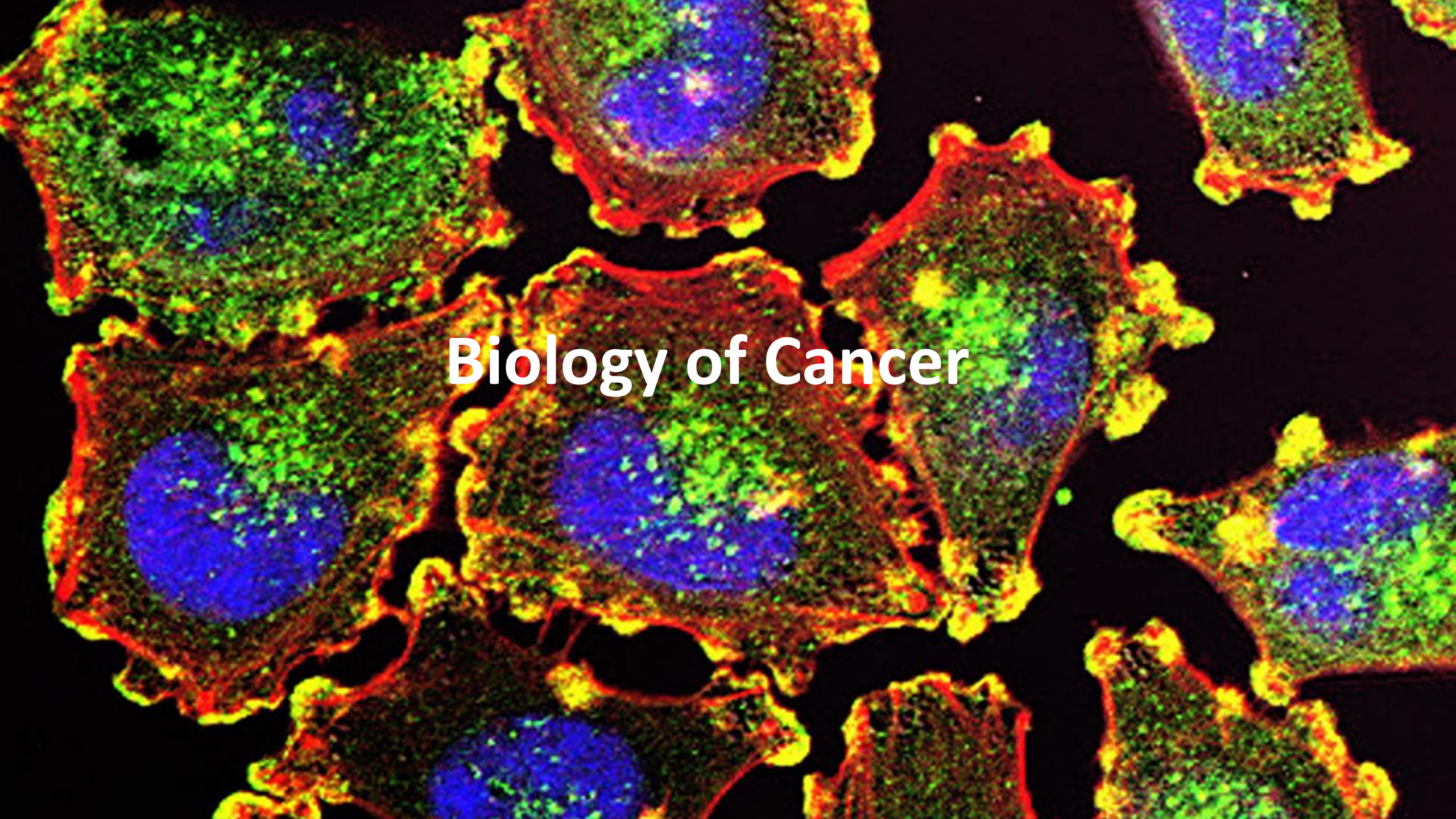
ECOLOGY AND EVOLUTION OF CANCER



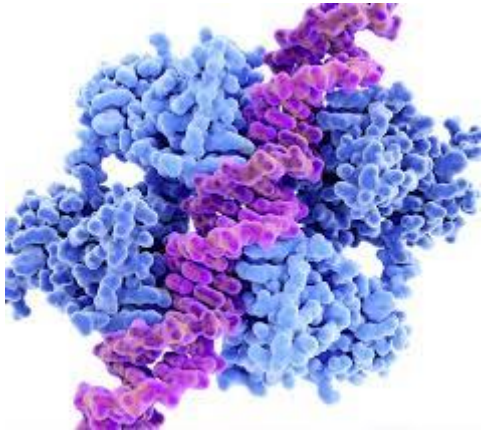
Cancer is a disease of multicellular organisms, and examples of cancer or cancer-like disease can be found in many metazoan taxa, both invertebrate (nematodes and insects) and vertebrate (fish, amphibians, reptiles, birds, and mammals). Although plants do develop localized tumors, most often as a result of microbial infection, such growths are unlikely to spread to other parts of the plant because plant cells are held in place by rigid cell walls that do not allow migration.

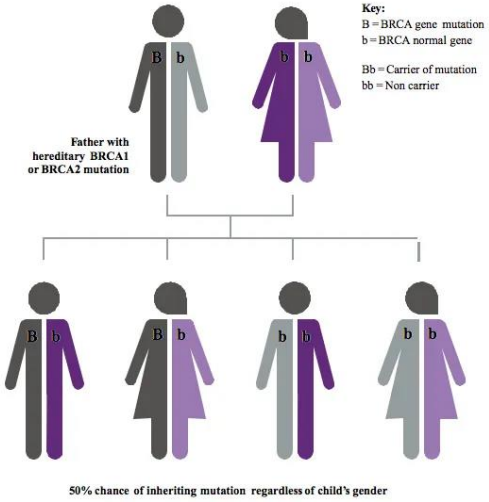
The transition from unicellular to multicellular organisms, which occurred several times around 600–1000 Mya in different lineages that gave rise to present-day animals and plants, required the evolution of mechanisms to promote cooperation among collections of cells. How this originated is unclear, but one example may be illuminating. In the multicellular alga *Volvox*, the gene controlling cell differentiation to produce germline (reproductively active) and somatic (body) cells has been co- opted from a similar gene in a unicellular ancestor that controls life-history decisions (survival versus reproduction) in response to environmental cues (see Hanschen et al. 2014). As organisms became more complex, mechanisms evolved to allow temporal and spatial control of cellular division, differentiation, and migration to produce function-specific tissues and organs. These mechanisms include limitations on the ability of some cell lineages to divide indefinitely, a range of internal quality control mechanisms that identify and destroy damaged cells that might proliferate uncontrollably, epigenetic control of differentiation into particular cell lineages, and sensitivity to physical and chemical growth signals generated from the surrounding tissue or from specialized remote tissues elsewhere in the organism. We consider how abrogation of these mechanisms characterizes some of the "hallmarks of cancer." Multicellularity involves a form of cellular altruism. All cells in a multicellular organism have the same genotype (but a different epigenotype), and multicellularity requires individual cells to cooperate in a way that allows the whole organism to represent the interests of the genotype; this involves limitations on the behavior and even the existence of particular single cells. Contrast this with the "selfish" ability of a single-celled organism to behave in whatever way optimizes the propagation of its genome. Cancer can be imagined as a re-adoption of such "selfish" behavior. The proliferating cancer cell outcompetes its neighboring normal cells and is thereby highly successful in the propagation of its particular genotype over a short timescale, but if its aberrant behavior kills the host the cancer genotype dies with it.



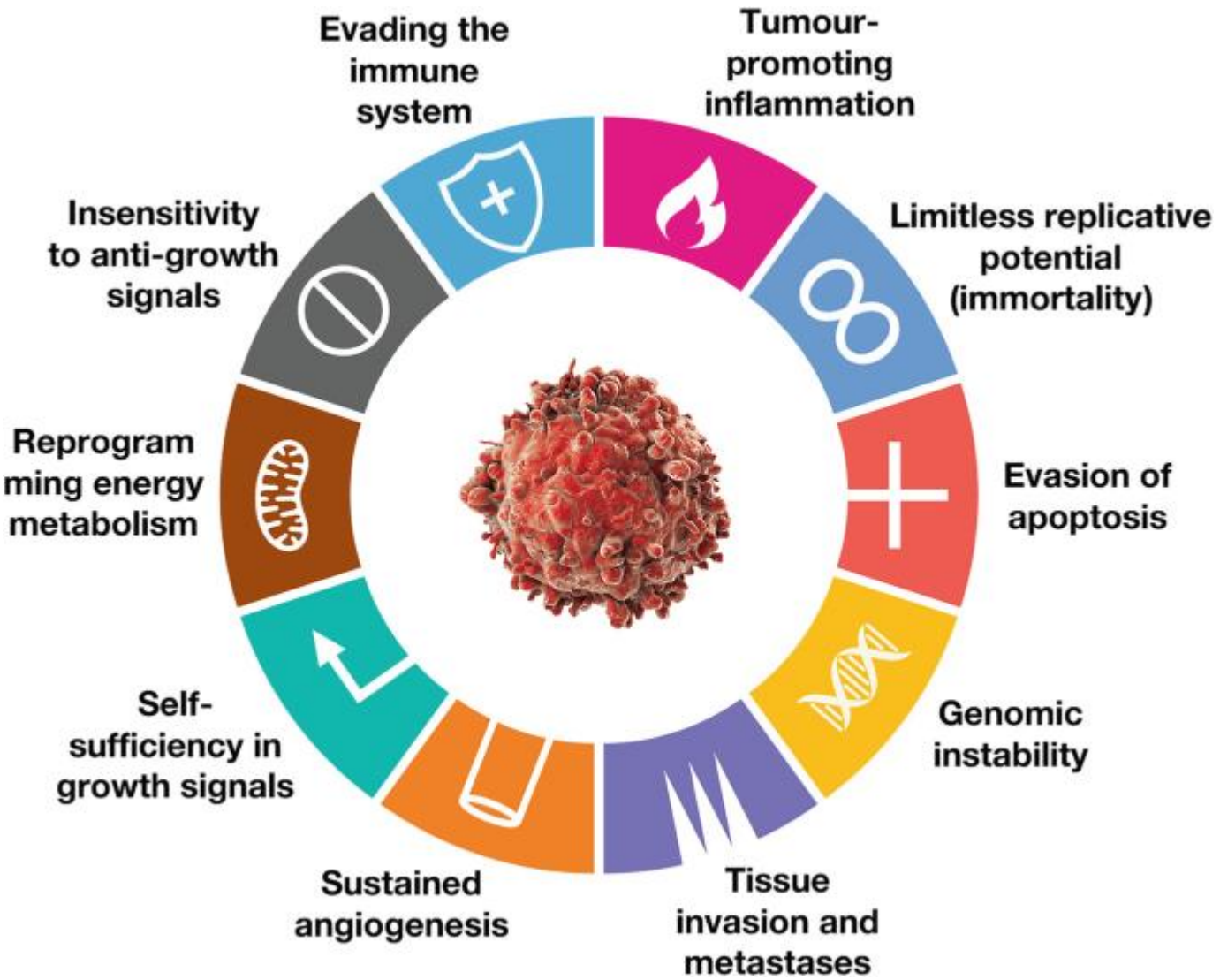

Biology of Cancer

Cancer is a disease characterized by the uncontrolled growth (malignant transformation followed by sustained proliferation) and spread (invasion and metastasis) of abnormal cells. The origin of a cancer is a single cell that acquires mutations that cause it to proliferate within its tissue at the expense of other cells, so in evolutionary terms the cancer cell has greater fitness.
There are two main types of genes implicated in the initial malignant transformation: oncogenes and tumor suppressor genes. In normal cells, proto-oncogenes (the “wild-type” precursors of oncogenes) are generally involved in growth-promoting pathways, whereas tumor suppressor genes are generally involved in repair or growth-limiting pathways. For example, the *HER-2/neu* gene codes for an epidermal growth factor receptor on the cell surface, and mutations that lead to overexpression of this protein, which are often found in breast cancer, cause cells to respond vigorously to the growth factor by proliferating. The drug trastuzumab (Herceptin®) blocks this pathway in individuals with this mutation. Conversely, the *p53* tumor suppressor gene, which is mutated in over 50% of human cancers, normally functions to limit proliferation by monitoring cellular stress and initiating DNA damage repair and cell cycle arrest if necessary.
Cells with typical cancer-associated mutations can be detected at a surprisingly high rate in early life—much higher than the incidence of their associated cancers—suggesting that further mutational “hits” to a particular cell during later life are required to generate a proliferating clone with a selective advantage (Mori et al. 2002). Although a cancer may involve hundreds or thousands of mutations, only relatively few (perhaps five or ten) actually act to “drive” tumor formation; among these, loss-of-function mutations in tumor suppressor genes are more common than activated oncogenes. It is these “driver” mutations that contribute to the increased fitness of a cancer cell in the tumor environment.
As the cancer cell clone expands, further mutations occur in particular cells to generate sub-clones with different genetic profiles that share only some of the “founder” mutations. Mutations in genes that enforce genetic stability, such as *p53* or *BRCA*, may in turn lead to sub-clones with a so-called “mutator phenotype,” having an increased mutation rate and an increased load of oncogenic mutations. In this way, a “successful” cancer acquires mutations that enable sub-clones to support vascularization, to break down physical barriers to allow expansion, and to evade the immune surveillance of its host organism. Stem cells are present in small numbers in normal adult tissue and allow a degree of tissue regeneration and repair. Stem cells are able to self - renew, possibly indefinitely, by mitotic division, but are also able to differentiate into the specialized progeny cells required for tissue replenishment. This differentiation means that the progeny cells also acquire replicative senescence and a limited lifespan, itself a tumor-suppressing mechanism. Since tissue stem cells already possess the capacity for self-renewal, they are likely candidates for the founder cells of a tumor if the mechanisms that normally control their self-renewal and induce differentiation are abrogated by driver mutations. Trade-offs between tissue repair capacity and susceptibility to cancer may be actualized by this role for stem cells in carcinogenesis. It remains unclear whether tumors contain particular subpopulations of cancer stem cells characterized by longevity and proliferative capacity that act as the key targets of selection, or whether all cancer cells have this property (Sprouffske et al. 2013). Certainly, primary tumors contain numerous types of non-cancer cells, including fibroblasts and epithelial cells, that together are termed the tumor stroma and that contribute to the microenvironment of the cancer cells. Because of their association with the cancer cells, these stromal cells acquire modified properties that contribute to tumor progression.





Hallmarks of Cancer



Although cancers can develop in most if not all tissues, and vary widely in their ability to proliferate and spread, all cancers share certain common traits at the molecular and cellular level (see Hanahan and Weinberg 2011). A general feature of these hallmarks of cancer, and one that was discussed earlier in the context of the origins of cancer, is that they concern the environment of, and the relationships between, cells in the context of organized tissues. In other words, they affect features of multicellular systems in which cells have evolved to cooperate and foster the interests of their genotype within a complex organism. These hallmarks include:

• *The ability to proliferate without the need for external growth signals.* Normal cells require a supply of growth factors for repeated cell division. Cancer cells do not, because they express their own, overexpress the receptors for those growth factors (e.g., HER- 2), or express mutated growth factor receptors that issue the "growth" signal without the need for an external ligand.

• *The ability to evade growth suppression*. The growth of normal cells is checked by negative signals from the extracellular matrix or from surrounding cells ("contact inhibition"). Cancer cells are insensitive to such signals.

• *Resistance to apoptosis (programmed cell death)*. Normal cells carry out a form of internal quality control, checking for events such as irreparable DNA damage or extreme hypoxia. Failing these checks causes the cell to undergo apoptosis. Cancer cells have defects in their apoptotic mechanism, causing them to become insensitive to apoptotic signals. The tumor suppressor gene *p53*, which undergoes loss- of- function mutation in many cancers, is part of the mechanism of programmed cell death, responsible for detecting DNA damage.

- *An unlimited ability to replicate*. Normal cells of most types cease to replicate after a certain number of divisions, a process mediated by the divisio-dependent shortening of DNA regions called telomeres at the end of chromosomes. In normal cells, the activity of the telomerelengthening enzyme telomerase is very low, but many cancer cells have increased levels of telomerase, which over- rides the shortening process and allows an unlimited number of cell divisions.

• *An increased ability to induce the formation of new blood vessels (angiogenesis).* The rapid proliferation of cancer cells can be resource- limited by the supply of nutrients and oxygen. Cancer cells develop the ability to promote angiogenesis, ensuring their continued growth. The importance of resource constraints in the ecology of tumors.

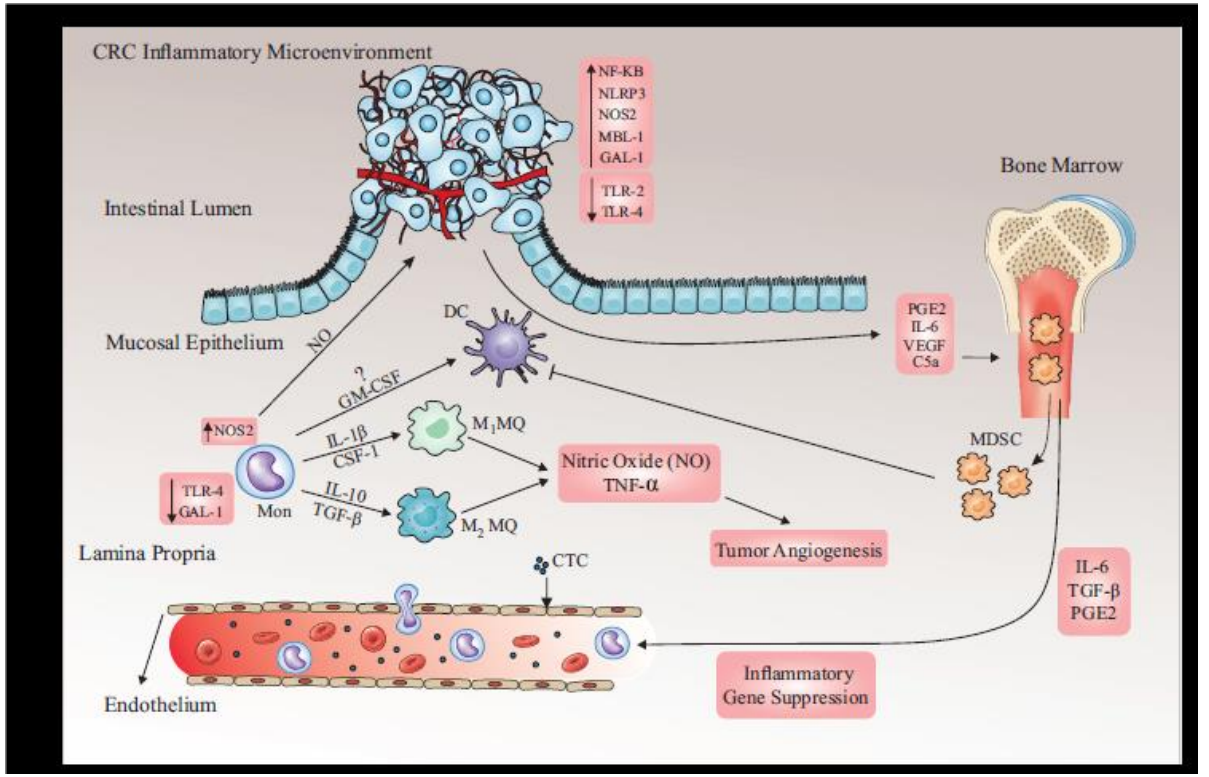
- *An uncontrolled capacity for invasion and metastasis*. The spread of cells within tissue, and their spread to other tissues, is normally tightly regulated by the control of cell– cell interactions via cell adhesion molecules, and by restricting the expression of enzymes that allow cells to move through the extracellular matrix. These control mechanisms are lost in cancer cells, allowing them to invade local tissue and to metastasize to distant sites. In particular, the increased capacity for tissue invasion appears to occur via co- option of an ancient cellular process essential for the formation of complex body patterns during embryonic development, termed the "epithelial– mesenchymal transition."

• *Altered energy metabolism*. Although cancer cells are able to induce angiogenesis to improve their supply of nutrients, some regions of solid tumors are often inadequately perfused and are nutrientand oxygen- poor. Under these conditions, cancer cells are often able to adapt by switching their metabolic pathways, particularly towards the use of anaerobic (non- oxygen- using) pathways such as glycolysis (the Warburg effect).

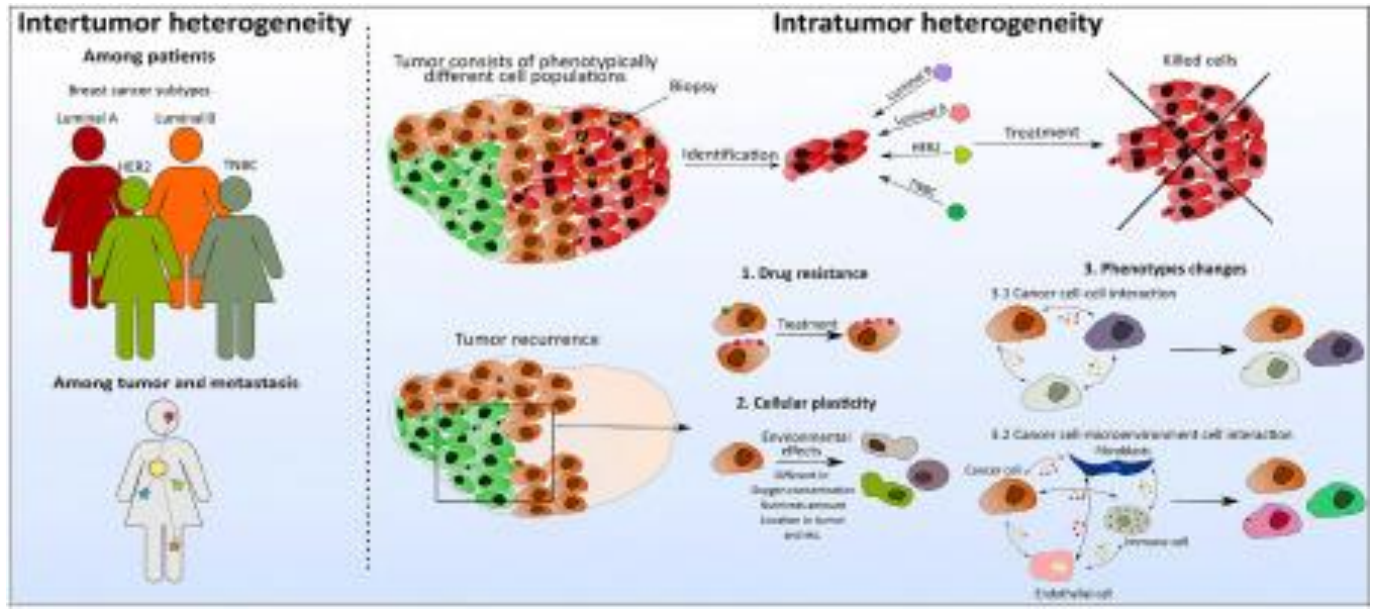
- *Evasion of immune- mediated attack*. The body's immune system can usually identify and destroy infected or damaged cells, and such immune surveillance is part of normal tumor suppression mechanisms. However, cancer cells can evade the body's immune system by mechanisms such as downregulating the expression of immunemediated molecules on their cell surface or by secreting immunosuppressive cytokines.

• *Genome instability*. Progression of a cell to the state of uncontrolled proliferation and migration characteristic of cancer requires several of the above hallmarks to be present, in turn requiring sequential accumulation of enabling mutations in the expanding cancerous clone. The underlying state facilitating this high rate of mutation is called genomic instability. Instability may occur at the nucleotide level, causing changes in the DNA sequence often associated with impaired DNA repair mechanisms, or at the chromosome level, causing deletion, duplication or inversion of whole chromosomes or chromosome segments. The *BRCA* genes, frequently mutated in several cancers in the context of life-history trade-offs in cancer, are involved in DNA repair.

• *Inflammation.* Another underlying characteristic of cancers is the role of local inflammation around the tumor site in promoting a facilitating environment for tumor growth and spread. Increased concentrations of inflammatory cells and pro-inflammatory cytokines at the tumor site may create conditions that promote tumor mutation, growth, and invasion.



Tumor Heterogeneity and its Consequences



Although cancers originate from a single cell with a discrete number of founder mutations, by the time a tumor is clinically apparent it will contain many billions of cells, each containing not only the founder mutations but also thousands more mutations acquired during rapid cellular proliferation. It is known that some bacteria are able to increase their mutation rate under stress, allowing more rapid adaptation to environmental events, but the existence of a similar “mutator phenotype” in cancer cells remains controversial. Some oncologists argue that the high prevalence in cancer cells of defects in DNA repair mechanisms, leading to high mutation rates andgenomic instability, is evidence of this phenotype, whereas others argue that the mutation rates observed in normal cells together with the high proliferation rate of cancer cells are sufficient to account for the multiple mutations found in tumors (see Fox et al. 2013).

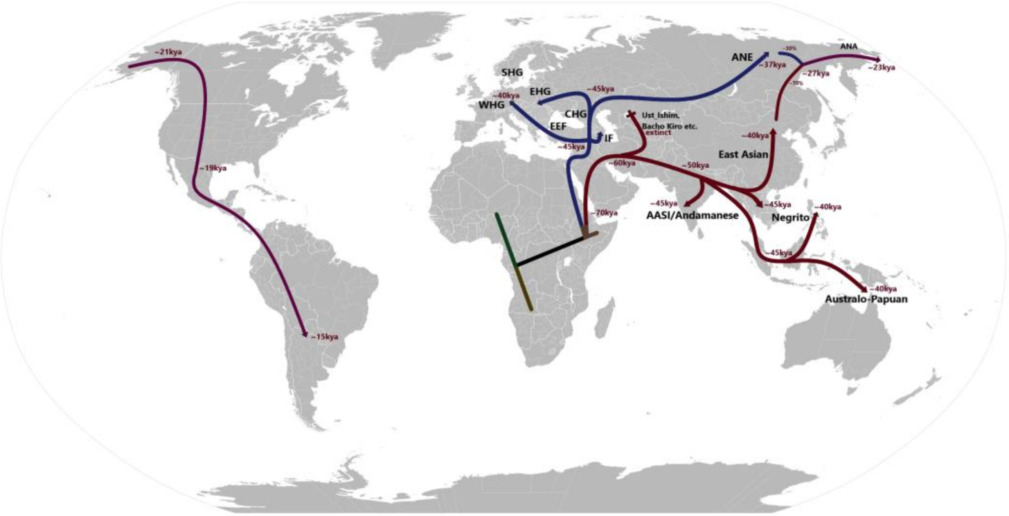
Nevertheless, the observation of a high mutational load in cancers, together with demonstration of mutations conferring resistance to chemotherapy in so far untreated tumors, and of early mutations promoting metastasis in primary tumors, underlines that tumors contain high levels of genetic variation. This variation is both heritable, as tumor cells divide mitotically into daughter cells, and clinically relevant in terms of disease progression and treatment. The existence of heritable (at a cellular level) genetic variation within a tumor implies that, if the tumor environment is not constant, some tumor cell clones will be at a selective advantage on the basis of their greater fitness within their current environment. The selective environment will vary spatially across the tumor depending on factors such as oxygen and nutrient availability, which in turn depend on proximity to the tumor vasculature. The presence of stromal and immune cells also contributes to the environment. Hence multiple sub-clones will exist within the tumor depending on their fitness in their particular microenvironment. Features of this intra-tumoral heterogeneity include different spatial patterns of mutation, convergent evolution (distinct mutations of the same tumor-suppressor genes in different parts of the tumor), and different prognostic signatures of gene expression in various tumor regions (see Gerlinger and Swanton 2010). The process leading to this heterogeneity has been termed *somatic evolution*. In addition to these microevolutionary events, macroevolutionary events analogous to speciation may lead to large changes in tumor phenotype, driven by genomic instability causing gross changes in the tumor genome, such as chromosomal rearrangements.

The success of chemotherapy, which applies a further selective pressure to the tumor, will depend on the relative fitness of susceptible and resistant clones. Tumors with high levels of genetic variation, and thus likely higher genetic instability that can be co-opted to evolve resistance mechanisms, would be predicted to be more resistant to chemotherapy. Moreover, if the bulk of tumor cells are sensitive to chemotherapy, killing them can provide resistant cells with a less-populated environment into which to expand. Finally, the process of metastasis can be seen as an evolutionary bottleneck analogous to a founder effect in the evolution of a population. Consequently, metastasized tumor cells will, at least initially, contain only a proportion of the genetic diversity of the primary tumor. Metastases are also faced with the challenge of adapting to their new tissue environment; this may result in the evolution of a set of mutations distinct from those in the primary tumor.

A Mismatched or Novel Environment

A number of cancers appear to arise because of exposure to environments or toxins which are novel in an evolutionary sense. One of the first cancers to have a specific etiology linked to an evolutionarily novel toxin was scrotal cancer in chimney sweeps, caused by exposure to tars in soot. The relationship between cigarette smoke, which is full of evolutionarily novel compounds such as inhaled tars, and lung cancer is well recognized. The risk of cancer associated with exposure to high levels of gamma radiation may simply reflect the truism that organisms have not evolved to live in an environment with high background radiation and thus do not have DNA repair mechanisms able to cope with the level of mutational injury caused. Different lifestyles across populations generate different risks of exposure to evolutionarily novel toxins, and these differences manifest themselves in the variable distribution of some. Pipe smoking is more likely to be associated with cancer of the lip and tongue, cigarette smoking with lung cancer, and tobacco chewing with oral cancer. The increase in meat consumption and reduction in dietary fiber has been linked to colon cancer (see O'Keefe et al. 2015). Highly salted and pickled foods have been associated with stomach cancer, and the marked reduction in the prevalence of gastric cancer in Europeans in recent decades has been postulated to be linked to the reductionin consumption of such foods. Excessive alcohol intake is associated with esophageal and stomach cancer, and possibly also with breast cancer.

Another example of the carcinogenic effects of novel environments is the high rates of skin cancer, including melanoma, seen in light-skinned northern Europeans who migrate to areas with high levels of ultraviolet exposure from sunlight (particularly Australia and New Zealand, where the atmospheric ozone barrier is reduced). Here we are seeing a double effect of migration: depigmented skin evolved in human populations who had migrated outside the tropics, probably to maintain vitamin D biosynthesis, and the reversal of that migration now results in high rates of skin cancer in those who lack the protective pigment melanin. As would be expected, migration into Australasia of darker-skinned individuals does not appear to increase their risk of skin cancer (e.g., Czarnecki 2014).
Hormone replacement therapy extends cyclic exposure to ovarian hormones beyond menopause and has been implicated in increased risk of reproductive cancers (see Chlebowski et al. 2003). Bisphenol A and a number of other plasticizer compounds as well as some pesticides can be estrogenic and or anti-androgenic, either directly or through their metabolites, and again may increase the risk of reproductive cancers (see Fenichel et al. 2013). Another factor may be the marked change in our nutrition, meaning that levels of growth-promoting hormones such as insulin-like growth factor 1 are higher from childhood and this may provide an environment in which clonal expansion of mutated cells is less restrained (see Cohen and LeRoith 2012). Finally, since most cancers are diseases of old age, it could simply be argued that just living longer allows more spontaneous somatic mutations to arise, as there has been greater cumulative exposure to environmental mutagens. In recent centuries, our average life expectancy has risen dramatically from a relatively constant figure over the previous 150,000 years. This, combined with the marked changes in the environments we inhabit (that may expose us to more mutagens), generates a simple stochastic model to explain the association between cancer and ageing.



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