"Cancer patients are lied to, not just because the disease is (or is thought to be) a death sentence, but because it is felt to be obscene – in the original meaning of that word: ill-omened, abominable, repugnant to the senses."

...Susan Sontag quotes
(American Writer Activist & Critic)
1993-2004
Cellular proliferation is a regulated process, which ensures that cell division is coordinated with physiological demands of the tissue or the organ. Under normal conditions, cells of adult body divide only to replace those cells that die (apoptosis) after fulfilling their task. Derangements of the regulatory mechanisms result in uncontrolled and excessive cellular proliferation—the cells are said to be malignantly transformed, and the condition is known as cancer (1). Lung, colorectal and stomach cancer are among the five most common cancers in the world for both men and women. Among men, lung and stomach cancer are the most common cancers worldwide. For women, the most common cancers are breast and cervical cancer (2). More than one mutation is necessary for carcinogenesis. In fact, a series of several mutations to certain classes of genes is usually required before a normal cell transforms into a cancer cell. Only mutations in those certain types of genes which play vital roles in cell division, cell death, and DNA repair will cause a cell to lose control of its proliferation.

The uncontrolled and often rapid proliferation of cells can lead to either a benign tumor or a malignant tumor (cancer). Benign tumors do not spread to other parts of the body or invade other tissues, and they are rarely a threat to life unless they extrinsically compress vital structures. Malignant tumors can invade other organs, spread to distant locations (metastasize) and become life-threatening.

Cancers are caused by a series of mutations.

\[ \text{Mutation inactivates tumor suppressor gene} \rightarrow \text{CELLS PROLIFERATE} \rightarrow \text{Mutations inactivate proto-oncogene} \rightarrow \text{DNA repair creates an oncogene} \rightarrow \text{Mutation inactivates several more tumor suppressor genes} \rightarrow \text{CANCER} \]
Proto-oncogenes promote cell growth through a variety of ways. Many can produce hormones, a "chemical messenger" between cells, which encourage mitosis, the effect of which depends on the signal transduction of the receiving tissue or cells. Some are responsible for the signal transduction system and signal receptors in cells and tissues themselves, thus controlling the sensitivity to such hormones. They often produce mitogens (is a chemical, usually some form of a protein that encourages a cell to commence cell division, triggering mitosis), or are involved in transcription of DNA in protein synthesis, which creates the proteins and enzymes responsible for producing the products and biochemicals cells use and interact with (3).

Mutations in proto-oncogenes can modify their expression and function, increasing the amount or activity of the product protein (4). When this happens, they become oncogenes, and thus cells have a higher chance to divide excessively and uncontrollably. The chance of cancer cannot be reduced by removing proto-oncogenes from the genome as they are critical for growth, repair and homeostasis of the body. It is only when they become mutated that the signals for growth become excessive.

Tumor suppressor genes code for anti-proliferation signals and proteins that suppress mitosis and cell growth. Generally tumor suppressors are transcription factors that are activated by cellular stress or DNA damage (5). Often DNA damage causes the presence of free-floating genetic material as well as other signs, and triggers enzymes and pathways which lead to the activation of tumor suppressor genes. The function of such genes is to arrest the progression of cell cycle in order to carry out DNA repair, preventing mutations from being passed on to daughter cells. Canonical tumor suppressors include the p53 protein, which is a transcription factor activated by many cellular stressors including hypoxia and ultraviolet radiation damage. Despite nearly half of all cancers may involve alterations in p53, its tumor suppressor function is poorly understood. p53 has two functions: one a nuclear role as a transcription factor, and the other a cytoplasmic role in cell cycle and division regulation and apoptosis.

p53 has been shown to regulate the shift from the respiratory to the glycolytic pathway (6). Synthesis of Cytochrome c Oxidase 2 (SCO2) has been recognized as the downstream mediator of this effect. SCO2 is critical for regulating the cytochrome c oxidase complex within the mitochondria, and p53 can disrupt the SCO2 gene. p53 regulation of
SCO2 and mitochondrial respiration may provide a possible explanation for the Warburg Effect (6).

In general, a mutation can damage the tumor suppressor gene itself, or the signal pathway which activates it, "switching it off". The invariable consequence of this is that DNA repair is hindered or inhibited: DNA damage accumulates without repair, inevitably leading to cancer. Thus, mutations in both types of genes are required for cancer to occur. For example, a mutation limited to one oncogene would be suppressed by normal mitosis control and tumor suppressor genes, which was first hypothesized as the Knudson hypothesis (7). A mutation to only one tumor suppressor gene would not cause cancer either, due to the presence of many "backup" genes that duplicate its functions. It is only when enough proto-oncogenes have mutated into oncogenes, and enough tumor suppressor genes deactivated or damaged, that the signals for cell growth overwhelm the signals to regulate it, that cell growth quickly spirals out of control. Often, because these genes regulate the processes that prevent most damage to genes themselves, the rate of mutations increase as one gets older, because DNA damage forms a feedback loop. Knudson's two hit model has recently been challenged by several investigators. Inactivation of one allele of some tumor suppressor genes is sufficient to cause tumors. This phenomenon is called haploinsufficiency and has been demonstrated by a number of experimental approaches. Tumors caused by haploinsufficiency usually have a later age of onset when compared with those by a two hit process (8).

Usually, oncogenes are dominant, as they contain gain-of-function mutations, while mutated tumor suppressors are recessive, as they contain loss-of-function mutations. Each cell has two copies of the same gene, one from each parent, and under most cases gain of function mutation in one copy of a particular proto-oncogene is enough to make that gene a true oncogene, while usually loss of function mutation needs to happen in both copies of a tumor suppressor gene to render that gene completely non-functional. However, cases exist in which one loss of function copy of a tumor suppressor gene can render the other copy non-functional. This phenomenon is called the dominant negative effect and is observed in many p53 mutations.

Mutation of tumor suppressor genes that are passed on to the next generation of not merely cells, but their offspring can cause increased likelihoods for cancers to be inherited. Members within these families have increased incidence and decreased latency of multiple
tumors. The mode of inheritance of mutant tumor suppressors is that affected member inherits a defective copy from one parent, and a normal copy from another. Because mutations in tumor suppressors act in a recessive manner (although there are exceptions), the loss of the normal copy creates the cancer phenotype. For instance, individuals who are heterozygous for \( p53 \) mutations are often victims of Li-Fraumeni syndrome, and those who are heterozygous for \( Rb \) mutations develop retinoblastoma. Similarly, mutations in the \( APC \) gene are linked to adenopolyposis colon cancer, with thousands of polyps in colon while young, while mutations in \( BRCA1 \) and \( BRCA2 \) lead to early onset of breast cancer.

Cancer pathology is ultimately due to the accumulation of DNA mutations that negatively effect expression of tumor suppressor proteins or positively effect the expression of proteins that drive the cell cycle. Substances that cause these mutations are known as mutagens, and mutagens that cause cancers are known as carcinogens. Particular substances have been linked to specific types of cancer. Tobacco smoking is associated with lung cancer. Prolonged exposure to radiation, particularly ultraviolet radiation from the sun, leads to melanoma and other skin malignancies. Breathing asbestos fibers is associated with mesothelioma. In more general terms, chemicals called mutagens and free radicals are known to cause mutations. Other types of mutations can be caused by chronic inflammation, as neutrophil granulocytes secrete free radicals that damage DNA. Chromosomal translocations, such as the Philadelphia chromosome, are a special type of mutation that involves exchanges between different chromosomes.

Many mutagens are also carcinogens, but some carcinogens are not mutagens. Examples of carcinogens that are not mutagens include alcohol and estrogen. These are thought to promote cancers through their stimulating effect on the rate of cell mitosis. Faster rates of mitosis increasingly leave fewer opportunities for repair enzymes to repair damaged DNA during DNA replication, increasing the likelihood of a genetic mistake. A mistake made during mitosis can lead to the daughter cells receiving the wrong number of chromosomes, which leads to aneuploidy and may lead to cancer.

Furthermore, many cancers originate from a viral infection; this is especially true in animals such as birds, but also in humans, as viruses are responsible for 15% of human cancers worldwide. The main viruses associated with human cancers are human papillomavirus, hepatitis B virus, Epstein-Barr virus, and human T-lymphotropic virus. Experimental and epidemiologic data imply a causative role for viruses and they appear to
be the second most important risk factor for cancer development in humans, exceeded only by tobacco usage (9). The mode of virally induced tumors can be divided into two, *acutely-transforming* or *slowly-transforming*. In acutely transforming viruses, the viral particles carry a gene that encodes for an overactive oncogene called viral-oncogene (v-onc), and the infected cell is transformed as soon as v-onc is expressed. In contrast, in slowly transforming viruses, the virus genome is inserted, especially as viral genome insertion is an obligatory part of retroviruses, near a proto-oncogene in the host genome. The viral promoter or other transcription regulation elements in turn cause overexpression of that proto-oncogene, which in turn induces uncontrolled cellular proliferation. Because viral genome insertion is not specific to proto-oncogenes and the chance of insertion near that proto-oncogene is low, slowly transforming viruses have very long tumor latency compared to acutely transforming viruses, which already carry the viral-oncogene.

It is impossible to identify the initial cause for any specific cancer. However, with the help of molecular biological techniques, it is possible to characterize the mutations or chromosomal aberrations within a tumor, and rapid progress is being made in the field of predicting prognosis based on the spectrum of mutations in some cases. For example, some tumors have a defective p53 gene. This mutation is associated with poor prognosis, since those tumor cells are less likely to go into apoptosis or programmed cell death when damaged by therapy. Telomerase mutations remove additional barriers, extending the number of times a cell can divide. Other mutations enable the tumor to grow new blood vessels to provide more nutrients, or to metastasize, spreading to other parts of the body.

**Malignant tumors cells have distinct properties:**

- evading apoptosis
- unlimited growth potential (immortalization) due to overabundance of telomerase
- self-sufficiency of growth factors
- insensitivity to anti-growth factors
- increased cell division rate
- altered ability to differentiate
• no ability for contact inhibition
• ability to invade neighboring tissues
• ability to build metastases at distant sites
• ability to promote blood vessel growth (angiogenesis)

A cell that degenerates into a tumor cell does not usually acquire all these properties at once, but its descendant cells are selected to build them. This process is called clonal evolution. A first step in the development of a tumor cell is usually a small change in the DNA, often a point mutation, which leads to a genetic instability of the cell. The instability can increase to a point where the cell loses whole chromosomes, or has multiple copies of several. Also, DNA methylation pattern of the cell changes, that activating and deactivating genes without the usual regulation. Cells that divide at a high rate, such as epithelial, show a higher risk of becoming tumor cells than those which divide less, for example neurons.