Cancer Fundamentals: Understanding The Big Picture

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FCA The National DABCI Schedule 2025

Friday 10:20- Noon (Clinical CE) Dr Kleber
Cancer Fundamentals: Understanding the Big Picture

Friday 1:00-2:40 (Clinical CE) Dr Wisniewski Immunopathology: Autoimmune Disease, Infection, Cancer Prevention and Recovery-Links, Triggers and Mechanisms

Friday 3:20-5:00 (Documentation)
Documenting the Chiropractic Physicians Role in Treating Cancer Patients

Saturday 10:20-Noon (Clinical CE)
Oxidative Load and Cancer: Understanding the Metabolic Links to Prevention and Progression

Saturday 1:00-2:40 (Clinical CE)
Conventional Diagnostics and Treatment of Cancer vs Alternative Diagnostics and Treatment of Cancer Patients

Saturday 3:20-5:00 (Documentation)
Documenting Integrative Medicine in Cancer: Enhancing Patient Outcomes Beyond Conventional Treatment

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The impact of cancer is immense in the U.S.

Cancer is the most feared disease.[1]

And is a leading cause of death in the U.S.[2]

1 in 3 people will be diagnosed with cancer in their lifetime[3]

1 in 5 people will die from cancer[3]

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The Chiropractic Physician and Cancer

- Chiropractic Physicians do not treat cancer.
- We treat people with cancer.
- We treat dysregulation.
- We treat chronic illness.
- We treat aberrant immune function. Viral infections.
- We improve detoxification.
- We remove nerve interference.
- We treat the patient as a whole.
- We focus on nutrition.
- We help the patient improve their energy (ATP).
- We help manage chronic illness "to a draw".

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NATIONAL CANCER INSTITUTE

Cancer Stats United States

- In 2025, the United States is projected to have 2,041,910 new cancer cases and 618,120 cancer deaths.
- Prostate, lung, and colorectal cancers account for an estimated 48% of all cancers diagnosed in men in 2025. For women, the three most common cancers are breast, lung, and colorectal, and they will account for an estimated 51% of all new cancer diagnoses in women in 2025.
- The incidence rate for new cancer cases is 445.8 per 100,000 people per year (based on 2018–2022 data), and the cancer death rate is 145.4 per 100,000 people per year (based on 2019–2023 data).
- Approximately 38.9% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2018–2021 data, not including 2020, due to COVID).

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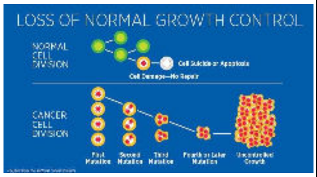
Cancer Definition

Cancer is a disease characterized by the uncontrolled growth and division of abnormal cells that can invade nearby tissues and spread to other parts of the body, a process known as metastasis. It can originate in almost any organ or tissue in the body. Normally, cells grow, divide, and die in an orderly way, but cancer cells ignore these controls, leading to the formation of tumors or, in some cases like blood cancers, abnormal cell growth without solid tumors. Tumors can be benign (non-cancerous) or malignant (cancerous), with malignant tumors having the ability to invade and spread.



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5 Year Survival Rate

The 5-year survival rate for cancer represents the percentage of people who are still alive five years after their cancer diagnosis. This statistic is widely used to give a general indicator of prognosis and to measure advances in cancer detection and treatment.

For all cancers combined in the United States, the current 5-year relative survival rate is approximately 69% for people diagnosed between 2014 and 2020. In the United Kingdom, the 5-year survival rate for all cancers combined for patients diagnosed in 2016 was reported as 55.7%.

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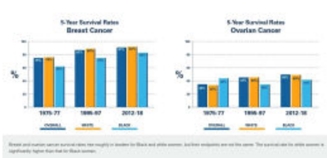
5 Year Survival Rate

The 5-year survival rates vary significantly depending on the type of cancer:

High survival rates: Testicular cancer (93.5%), melanoma (92.6%), prostate cancer (88.5%).

Low survival rates: Pancreatic cancer (8.3%), brain cancer (12.9%), liver cancer (13.4%).

For lung cancer, the 5-year survival rate can be less than 20%, with more advanced (late-stage) cases having rates as low as 7%



Dana-Farber Cancer Institute

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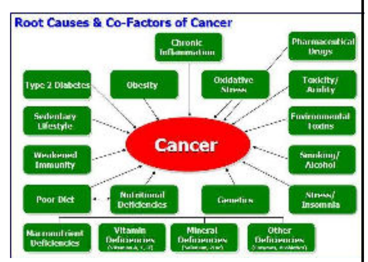
Causes of Cancer

Genetic mutation (inherited or induced)
Free radical
Excessive glucose
Drugs
Pesticides (a large increase for Parkinson's)
GMOs
Synthetic hormones (esp. long term administration)
Infections
Solar radiation
- Melanoma is most commonly found in areas that are not exposed to the sun- check the buttocks and in-between the toes of your patients.



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Cancer as a Chronic Disease

A chronic disease is considered an "illness that may develop slowly, last a long time, (from months to years), be incurable, and be progressive and/or life-limiting".

While some cancers can be cured, others cannot be fully eradicated and may persist for years, requiring ongoing treatment and monitoring. Examples include chronic leukemias, some lymphomas, ovarian cancer, metastatic breast and prostate cancers, and others. In these cases, the disease is controlled rather than cured, similar to how diabetes or heart disease is managed.

Sciences:, R. o. t. E. P. a. b. t. C. A. o. H. Transforming care for Canadians with chronic health conditions: Put people first, expect the best, manage for results. Ottawa Ontario: Canadian Academy of Health Sciences; 2010.

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Cancer as a Chronic Disease

Advances in cancer treatments—such as targeted therapies, immunotherapies, and improved supportive care—have enabled many patients to live longer with cancer, transforming it from an acute, often terminal diagnosis into a manageable, long-term condition for many.

Brenner DR, Weir HK, Demers AA, Ellison LF, Louzado C, Shaw A, Turner D, Woods RR, Smith LM Canadian Cancer Statistics Advisory C. Projected estimates of cancer in Canada in 2020. CMAJ. 2020;192(9):E199–E205. doi: 10.1503/cmaj.191292.

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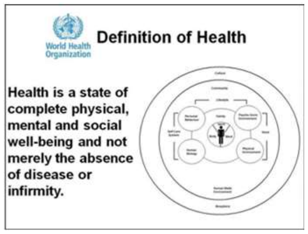
Can Cancer be Cured?

Cure usually refers to a complete restoration of health, while *treatment* refers to a process or procedure that leads to an improvement in health or the recovery from injury. *Cure* comes from the Latin word meaning "to care," and *treat* shares Latin roots with words that refer to written documents like *treaty* and *tract*.



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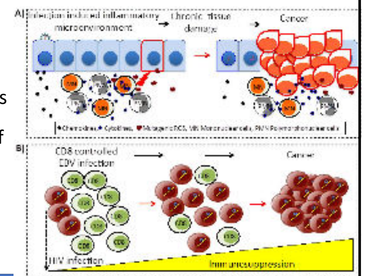
Viruses and Cancer

Transformation by a virus may be defined as changes in the biologic function of a cell that results from regulation of the cell by viral genes that confer on the infected cell certain properties characteristic of neoplasia.

These changes often(but not always) result from integration of the viral genome into the host cell genome.



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Viruses and Cancer

Certain families of viruses can infect vertebrate cells and transform them into cancer cells.

The transforming viruses have been divided into 2 groups on the basis of their genomic nucleic acid.

1) DNA tumor viruses
2) RNA tumor viruses

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Viruses and Cancer

DNA tumor viruses: The viruses that contain DNA as their genetic material and induce tumors are called DNA Tumor viruses.

- For example, Papova virus(SV,40, polyoma and papilloma virus) Adenovirus, Herpes virus Poxviruses and hepatitis B virus.

RNA : tumor viruses (Retroviruses)

All RNA tumor viruses belong to the retrovirus family.

They cause adult T-cell leukemia in humans.

A retrovirus is a type of virus that uses RNA as its genetic material instead of DNA. When it infects a cell, it uses an enzyme called reverse transcriptase to convert its RNA into DNA. This viral DNA then integrates into the host cell's DNA, allowing the virus to replicate and spread. A well-known example is HIV, the virus that causes AIDS.

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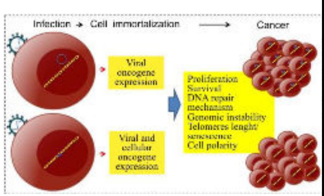
Viral Infections as a Cause of Cancer

Infections: Certain viruses, bacteria, and parasites can increase cancer risk. Notable examples include:

- Human papillomavirus (HPV) for cervical cancer,
- Hepatitis B and C viruses for liver cancer,
- Helicobacter pylori for stomach cancer,
- Epstein-Barr virus for several cancers.



(2) de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020;8(2):e180-e190.

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American Cancer Society

Examples of Viral Infections Causing Cancer

- Human papillomavirus (HPV): Certain types of HPV are strongly linked to cervical cancer, as well as cancers of the anus, penis, vulva, vagina, and oropharynx.
- Epstein-Barr virus (EBV): Associated with Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, and certain stomach cancers.
- Hepatitis B virus (HBV) and Hepatitis C virus (HCV): Both viruses can cause chronic liver infection, significantly increasing the risk of hepatocellular carcinoma (liver cancer).
- Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV): Causes Kaposi sarcoma and some types of lymphoma, particularly in immunocompromised individuals.
- Merkel cell polyomavirus (MCV): Linked to Merkel cell carcinoma, a rare but aggressive form of skin cancer.
- Human T-lymphotropic virus type 1 (HTLV-1): Causes adult T-cell leukemia/lymphoma.

Human Immunodeficiency Virus (HIV) does not directly cause cancer, but it weakens the immune system, increasing susceptibility to cancers caused by other oncogenic viruses.

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Examples of Viral Infections Causing Cancer

Human Papilloma Virus are a group of more than 150 related viruses. They are called *papillomaviruses* because some of them cause papilloma's, which are more commonly known as warts. Some types of HPV only grow in skin, while others grow in mucous membranes such as the mouth, throat, or vagina.

All types of HPV are spread by contact. More than 40 types of HPV can be passed on through sexual contact. Most sexually active people are infected with one or more of these HPV types at some point in their lives. At least a dozen of these HPV types are known to cause cancer.

While HPV infections are very common, cancer caused by HPV is not. Most people infected with HPV will not develop a cancer related to the infection. However, some people with long-lasting infections of high-risk HPV types are at risk of developing cancer..

HPV infections of the mucous membranes can cause genital warts, but they usually have no symptoms. There are no effective medicines or other treatments for HPV, other than removing or destroying cells that are known to be infected. But in most people, the body's immune system controls the HPV infection or gets rid of it over time

A few types of HPV are the main causes of cervical cancer, which is the second most common cancer among women worldwide. Cervical cancer has become much less common in the United States because the Pap test has been widely available for many years. This test can show pre-cancer in cells of the cervix that might be caused by HPV infection. These pre-cancer cells can then be destroyed or removed, if needed.

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Examples of Viral Infections Causing Cancer

Epstein-Barr virus (EBV)

EBV type of herpes virus. It is probably best known for causing infectious mononucleosis. Most people in the United States are infected with EBV by the end of their teen years, although not everyone develops the symptoms of mono.

As with other herpes virus infections, EBV infection is life-long, even though most people have no symptoms after the first few weeks. EBV infects and stays in *B lymphocytes*. There are no medicines or other treatments to get rid of EBV, nor are there vaccines to help prevent it, but EBV infection doesn't cause serious problems in most people.

EBV infection increases a person's risk of getting nasopharyngeal cancer and certain types of fast-growing lymphomas such as Burkitt lymphoma. It may also be linked to Hodgkins lymphoma and some cases of stomach cancer. EBV-related cancers are more common in Africa and parts of Southeast Asia. Overall, very few people who have been infected with EBV will ever develop these cancers.

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Examples of Viral Infections Causing Cancer

Hepatitis B virus (HBV) and hepatitis C virus (HCV)

Both HBV and HCV cause viral hepatitis. Other viruses can also cause hepatitis (hepatitis A virus, for example), but only HBV and HCV can cause the chronic infections that increase a person's chance of hepatocellular carcinoma. In the United States, less than half of liver cancers are linked to HBV or HCV infection. But this number is much higher in some other countries, where both viral hepatitis and liver cancer are much more common. Some research also suggests that long-term HCV infection might be linked with some other cancers, such as non-Hodgkin lymphoma.

HBV and HCV are spread from person to person in much the same way as HIV — through sharing needles, unprotected sex, or childbirth. They can also be passed on through blood transfusions.

Of the 2 viruses, infection with HBV is more likely to cause symptoms, such as a flu-like illness and jaundice. Most adults recover completely from HBV infection within a few months. Only a very small portion of adults go on to have chronic HBV infections, but this risk is higher in young children. People with chronic HBV infections have a higher risk for liver cancer.

HCV is less likely to cause symptoms than HBV, but it is more likely to cause chronic infection, which can lead to liver damage or even cancer. Millions of people in the United States have chronic HCV infections, and most of these people don't even know they have it.

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Examples of Viral Infections Causing Cancer

Human immunodeficiency virus (HIV)

HIV, the virus that causes acquired immune deficiency syndrome (AIDS), doesn't appear to cause cancers directly. But HIV infection increases a person's risk of getting several types of cancer, especially some linked to other viruses.

HIV can be spread through semen, vaginal fluids, blood, and breast milk from an HIV-infected person. Known routes of spread include:

Injections with needles or injection equipment previously used by an HIV-infected person

Prenatal (before birth) and perinatal (during birth) exposure of infants from mothers with HIV

Breastfeeding by mothers with HIV

Penetrating injuries or accidents (usually needle sticks) in health care workers while caring for HIV-infected patients or handling their blood

HIV infects and destroys white blood cells known as helper T-cells, which weakens the body's immune system. This might let some other viruses, such as HPV, thrive, which might lead to cancer.

Many scientists believe that the immune system is also important in attacking and destroying newly formed cancer cells. A weak immune system can contribute to cancer.

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Examples of Viral Infections Causing Cancer

Human herpes virus 8 (HHV-8)

HHV-8, also known as Kaposi sarcoma–associated herpes virus (KSHV), has been found in nearly all tumors in patients with Kaposi sarcoma (KS). KS is a rare, slow-growing cancer that often appears as reddish-purple or blue-brown tumors just underneath the skin. In KS, the cells that line blood and lymph vessels are infected with HHV-8. The infection makes them divide too much and live longer than they should. These types of changes may eventually turn them into cancer cells.

HHV-8 is transmitted through sex and appears to be spread other ways, such as through blood and saliva, as well. Studies have shown that fewer than 10% of people in the US are infected with this virus.

HHV-8 infection is life-long (as with other herpes viruses), but it does not appear to cause disease in most healthy people. Many more people are infected with HHV-8 than ever develop KS, so it's likely that other factors are also needed for it to develop. Having a weakened immune system appears to be one such factor.

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Examples of Viral Infections Causing Cancer

Human T-lymphotrophic virus-1 (HTLV-1)

HTLV-1 has been linked with a type of lymphocytic leukemia and non-Hodgkin lymphoma called adult T-cell leukemia/lymphoma (ATL). This cancer is found mostly in southern Japan, the Caribbean, central Africa, parts of South America, and in some immigrant groups in the southeastern United States.

In addition to ATL, this virus can cause other health problems, although many people with HTLV-1 don't have any of them.

HTLV-1 belongs to a class of viruses called *retroviruses*.

HTLV-1 is something like HIV, which is another human retrovirus. But HTLV-1 cannot cause AIDS. In humans, HTLV-1 is spread in the same ways as HIV, such as unprotected sex with an HTLV-1-infected partner or injection with a needle after an infected person has used it. Mothers infected with HTLV-1 can also pass on the virus to their children, although this risk can be reduced if the mother doesn't breastfeed.

Infection with HTLV-1 is rare in the United States. Fewer than 1% of people in the US are infected with HTLV-1, but this rate is much higher in groups of people at high risk.

Once infected with HTLV-1, a person's chance of developing ATL can be up to about 5%, usually after a long time with no symptoms (20 or more years).

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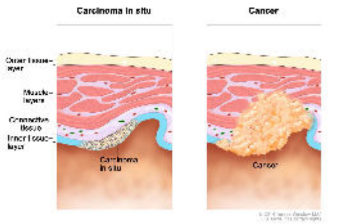
5 Basic Forms of Cancer: Carcinoma

Carcinoma: The most common type of cancerous growth. Solid tumors that can affect almost any organ or part of the body. Can metastasize via the lymphatic system or bloodstream. Form in the epithelial cells which cover the surface of the body and line body cavities, tubes and passageways leading to the exterior. Include skin, mouth, nose, throat lungs, GU and GI tracts and glands such as the breasts or thyroid.



Carcinoma in situ (CIS) refers to a group of abnormal cells that are confined to their original location and haven't spread to surrounding tissues.

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Common Types of Carcinoma

Squamous cell carcinoma: This affects the flat, scale-like squamous cells of the skin, respiratory and digestive tracts, and the lining of hollow organs like the cervix and vagina. It is often found on sun-exposed areas.

Basal cell carcinoma: This is the most common type of skin cancer. It starts in the basal cells, found in the deepest layer of the skin, and typically appears on sun-exposed areas like the face, ears, neck, and shoulders.

Adenocarcinoma: This type develops in glandular cells, which produce fluids like mucus and digestive juices. Examples include lung, breast, colon, and prostate cancers.

- Transitional cell carcinoma: This cancer originates in transitional cells, which can stretch and are found in the lining of the bladder, ureters, and renal pelvis. It is also known as urothelial carcinoma.
- Renal cell carcinoma: This is the most common type of kidney cancer, typically developing in the lining of the kidney tubules.
- Invasive ductal carcinoma: This type of breast cancer begins in the milk ducts and spreads into surrounding breast tissue. It is the most common type of breast cancer.
- Ductal carcinoma in situ: This is considered a noninvasive or pre-invasive type of breast cancer, where the abnormal cells are confined to the milk ducts and have not spread.

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5 Basic Forms of Cancer: Leukemias

Leukemias: form in the blood and bone marrow and are not solid tumors. The abnormal white blood cells associated with leukemias replace healthy white blood cells and then circulate throughout the bloodstream.

- Symptoms: Fatigue, Weakness, Bruising easily, Bleeding gums or nose, Frequent infections, Fever, Night sweats, and Weight loss.
- Labs: High WBC's, low RBC's and low platelets.

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5 Basic Forms of Cancer: Myeloma

Myelomas: are tumors that originate in plasma cells, the antibody-producing white blood cells in a portion of the bone marrow. Myelomas were formerly considered rare, but their incidence is increasing.

Plasma cells are differentiated B-lymphocyte white blood cells capable of secreting immunoglobulin or antibodies.

- Bone pain and fractures
- Fatigue and weakness
- Hypercalcemia
- Kidney problems
- Increased risk of infection
- Peripheral neuropathy

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5 Basic Forms of Cancer: Lymphoma

Lymphomas: cancers found in the glands and nodes of the lymphatic system. Lymph nodes are found in the neck, groin, armpits, spleen, center of the chest, and around the intestines. Lymphomas are solid tumors usually made up of abnormal white blood cells. Hodgkin's and non-Hodgkin's lymphoma are the most common forms of lymphatic cancer in the United States.

- Painless swelling of lymph nodes (especially in the neck, armpits, or groin),
- Fever
- Night sweats
- Fatigue
- Unexplained weight loss

Labs: Elevated LDH and Sed Rate
Decreased WBC and/or platelets
Biopsy needed for DDX.

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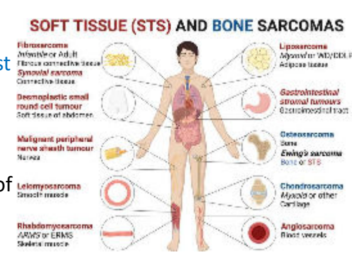
5 Basic Forms of Cancer: Sarcoma

Sarcomas: are the rarest of the five types and can entail the most challenging prognosis. Sarcomas are solid tumors that arise from connective tissue, such as bone and muscle. Sarcomas can also form in the surrounding tissues of major organs. Found in arms or legs in 60% of the cases



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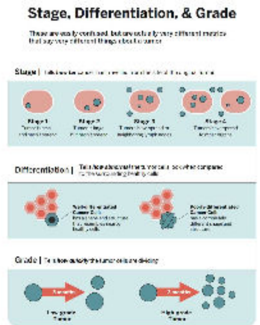
Grades of Cancer

- **Grade 1:** Cancer cells look very similar to normal cells and tend to grow slowly.
- **Grade 2:** Cancer cells don't look like normal cells and are growing faster than normal cells.
- **Grade 3:** Cancer cells look abnormal and may grow and/or spread quickly.
- **Grade 4:** Cancer cells are undifferentiated and highly aggressive, meaning they grow and spread rapidly.

The higher the grade, the more undifferentiated, aggressive, and difficult to treat the cancer is.



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Stages of Cancer

Staging allows for determination of a prognosis and regimen of treatment. The stage is based on the tumor's size, location, and whether it has spread. If more than one tumor is present, the largest tumor determines the stage.

- Stage I = the earliest, most curable, with only local tissue involvement
- Stage II = cancer has spread to some surrounding tissues & possibly to nearby lymph nodes
- Stage III = cancer has metastasized to distant lymph nodes
- Stage IV = cancer has spread to distant organs or other parts of the body; this stage is the most advanced and difficult to treat

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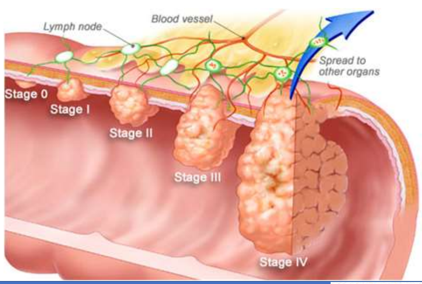
Stages of Cancer



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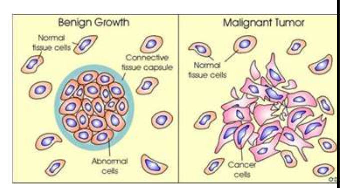
Benign vs. Malignant

Benign- cells that closely resemble and/or may function like normal cells

- Benign tumor know boundaries and stay within the organ of origin usually delineate with a fibrous capsule
- "Benign tumors become serious medical problems only if their sheer bulk interferes with normal functions or if they secrete excess amounts of biologically active substances like hormones."



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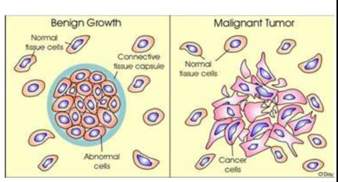
Benign vs. Malignant

Malignant- express similar characteristics to cell type of origin

- Some tumors remain encapsulated, others invaded surrounding tissues
- Most malignant cells have the ability of metastasis
- Microscopic exam are not well differentiated vs. normal cells
  - High nucleus to cytoplasm ratio (rapidly growing cells)



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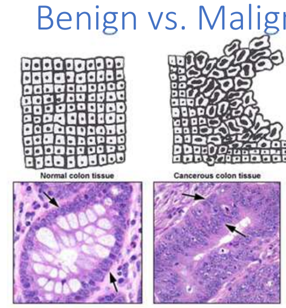
Benign vs. Malignant



High Nucleus-cytoplasm ratio

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Cell-to-Cell Interaction- Malignancy/ Metastasis

- Normal cells reside within in a physical barrier- basal lamina (*basement membrane*)
- Malignant tumor cells increase production of proteases which break down the basal lamina and allow cells to enter circulation
  - It is estimated that only 1 in 10,000 cells that break through the basement membrane will make it to the secondary site

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Angiogenesis/ Metastasis

Angiogenesis is the physiological process through which new blood vessels are formed from pre-existing vessels.

It involves the migration, growth, and differentiation of endothelial cells, resulting in the development of new capillaries or microvascular structures

This process is essential for normal growth, development, and wound healing, as it provides tissues and organs with an increased blood supply of oxygen and nutrients.

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Signals and Factors that Regulate Angiogenesis

- Vascular Endothelial Growth Factor (VEGF): This is the most crucial stimulator of angiogenesis, directly promoting the proliferation, migration, and survival of endothelial cells that form new blood vessels. Its action is enhanced by low oxygen, through activation by hypoxia-inducible factor-1 alpha (HIF-1α).
- Fibroblast Growth Factor (FGF): FGFs (especially FGF-2 or bFGF) are potent promoters of endothelial cell proliferation and differentiation, participating in wound healing and tissue repair.
- Angiopoietins (especially Ang-1 and Ang-2): These factors work with their Tie receptors to stabilize and mature blood vessels, control permeability, and mediate remodeling of existing vasculature.
- Platelet-Derived Growth Factor (PDGF): Recruits supporting pericytes and smooth muscle cells to new vessels, stabilizing the developing vasculature.
- Hypoxia/ HIF-1α: Low oxygen levels in tissues upregulate HIF-1α, which stimulates the production of VEGF and other pro-angiogenic genes, serving as a central environmental trigger for angiogenesis.
- Nitric Oxide (NO): Produced by endothelial cells, NO mediates vasodilation and contributes to angiogenic signaling cascades, including downstream effects of VEGF.
- Anti-angiogenic factors: To balance vessel growth, inhibitors like thrombospondin, angiostatin, and endostatin suppress excessive or abnormal blood vessel formation.

Angiogenic signaling pathways and anti-angiogenic therapy for cancerhen-Ling Liu, Huan-Huan Chen, Li-Li Zheng, Li-Ping Sun & Lei Shi *Signal Transduction and Targeted Therapy* **volume 8**, Article number: 198 (2023)

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Pericytes

Pericytes are cells present at intervals along the walls of capillaries (and post-capillary venules). In the CNS, they are important for blood vessel formation, maintenance of the blood–brain barrier, regulation of immune cell entry to the central nervous system (CNS) and control of brain blood flow.

Dalkara T, Gursoy-Ozdemir Y, Yemisci M. Brain microvascular pericytes in health and disease. Acta Neuropathol 2011; 122: 1–9.

Pericytes, spatially isolated contractile cells on capillaries, have been reported to control cerebral blood flow physiologically, and to limit blood flow after ischemia by constricting capillaries and then dying.

Pericytes also play a key role in pathology: in ischemia pericytes constrict capillaries, trapping blood cells, which prevents microcirculatory reperfusion after clot removal in stroke.

Hall CN, Reynell C, Gesslein B, et al. Capillary pericytes regulate cerebral blood flow in health and disease. Nature 2014; 508: 55–60.

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Angiogenesis

Growing tumor cells stimulate angiogenesis to supply the mass with nutrients

- Break down of the basal lamina
- Secretion of growth factors
  - Basic fibroblast growth factor (bFGF)
  - Transforming growth factor (TGFα)
  - Vascular endothelial growth factor (VEGF)

> One of the most mysterious aspects of angiogenesis is that a primary tumor will often secrete a substance that inhibits angiogenesis around secondary metastases. In this case, surgical removal of the primary tumor may stimulate growth of its metastatic secondary tumors.

Lodish H, Berk A, Zipursky SL, et al. Molecular Cell Biology. 4th edition. New York: W. H. Freeman; 2000. Section 24.1, Tumor Cells and the Onset of Cancer. Available from: https://www.ncbi.nlm.nih.gov/books/NBK21590/

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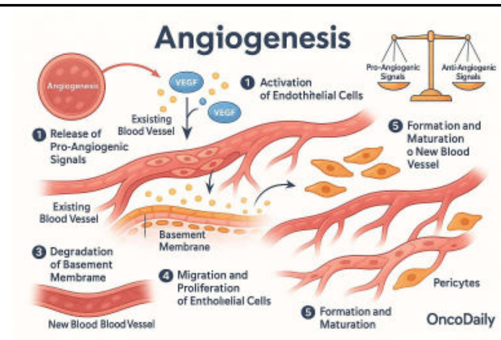

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Disruption of Angiogenesis

Angiogenesis is governed by the balance between pro-angiogenic factors (notably VEGF, FGF, angiopoietins, and PDGF), anti-angiogenic molecules (e.g., thrombospondin, endostatin), and oxygen levels, primarily coordinated through HIF-1α and its downstream targets.

HIF-1alpha is a protein that plays a role in how cells respond to low oxygen levels

Angiogenic signaling pathways and anti-angiogenic therapy for cancerhen-Ling Liu, Huan-Huan Chen, Li-Li Zheng, Li-Ping Sun & Lei Shi *Signal Transduction and Targeted Therapy* **volume 8**, Article number: 198 (2023)

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Avastin

- Avastin (generic name: bevacizumab) is a prescription medication classified as a monoclonal antibody and an angiogenesis inhibitor. It is primarily used to treat several types of cancers, including:
- Metastatic colorectal cancer (mCRC)
- Non-squamous non-small cell lung cancer (NSCLC)
- Glioblastoma (a type of brain tumor)
- Metastatic renal cell carcinoma
- Cervical, ovarian, fallopian tube, and peritoneal cancers
- In combination with atezolizumab, for hepatocellular carcinoma in certain patients.

HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use AVASTIN safely and effectively. See full prescribing information for AVASTIN. AVASTINâ (bevacizumab) injection, for intravenous use Initial U.S. Approval: 2004

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Avastin

Avastin works by inhibiting vascular endothelial growth factor A (VEGF-A), a protein that stimulates the growth of new blood vessels (angiogenesis). By blocking VEGF-A, Avastin restricts the tumor's blood supply, slowing its growth and potentially shrinking the tumor. It does not act as traditional chemotherapy but is often given alongside chemotherapy or other cancer treatments.

Common side effects:

- Nose bleeds
- Headache
- High blood pressure
- Fatigue
- Rash

Serious risks include:

Gastrointestinal perforations
Bleeding and blood clots
Impaired wound healing
Formation of fistulae (abnormal connections between organs)
Increased risk of infection

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Avastin

Gastrointestinal Perforations and Fistula: Discontinue for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any organ (5.1) • Surgery and Wound Healing Complications: In patients who experience wound healing complications during Avastin treatment, withhold Avastin until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days following a major surgery, and until adequate wound healing. The safety of resumption of AVASTIN after resolution of wound healing complication has not been established. Discontinue for wound healing complication of necrotizing fasciitis. (5.2) • Hemorrhage: Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 3-4 hemorrhage (5.3) • Arterial Thromboembolic Events (ATE): Discontinue for severe ATE. (5.4) • Venous Thromboembolic Events (VTE): Discontinue for Grade 4 VTE. (5.5) • Hypertension: Monitor blood pressure and treat hypertension. Withhold if not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy. (5.6) • Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue. (5.7) • Renal Injury and Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Withhold until less than 2 grams of protein in urine. (5.8) • Infusion-Related Reactions: Decrease rate for infusion-related reactions. Discontinue for severe infusion-related reactions and administer medical therapy. (5.9) • Embryo-Fetal Toxicity: May cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception. (5.10, 8.1, 8.3) • Ovarian Failure: Advise females of the potential risk. (5.11, 8.3) • Congestive Heart Failure (CHF): Discontinue Avastin in patients who develop CHF. (5.12)

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Avastin

VEGF-A signals by binding to receptors on endothelial cells, triggering downstream pathways that promote cell proliferation and migration.

L Citrulline

L Arginine

Dietary nitrates
(green leafy veggies and root veggies like beets and celery).

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Oncogenes and Tumor Suppressor Genes

There may be as few as 40 cellular genes in which mutation or some other disruption of their expression leads to unrestricted cell growth.

There are two classes of these genes in which altered expression can lead to loss of growth control.

1) Oncogene

2) Tumor suppressor gene

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Oncogenes and Tumor Suppressor Genes

Oncogene: genes stimulatory for growth can cause cancer when hyperactive mutations in these genes become active.

Oncogene discovered in 1970.

Tumor suppressor gene:

Genes that inhibit cell growth which cause cancer when they are turned off. They are recessive. When tumor suppressor genes don't work properly, cells can grow out of control and can lead to cancer or malignancy.

Cancer tries to hijack these mechanisms.

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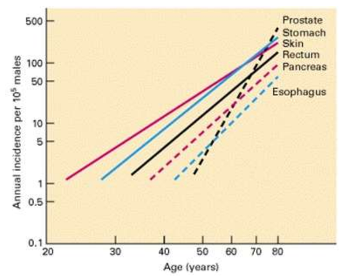
Aging and Cancer



As we age the incidence of cancer goes up

a. Vogelstein and K. Kinzler, 1993, Trends Genet. 9:101

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Genetics

3 main mechanisms of how genetics are involved

1) Blocking or silencing anti-cancer/tumor suppressor genes
2) Activation of carcinogenic genes
3) Loss of function of stability genes
   - ie: Smoking and defects in GSTP, CYP…

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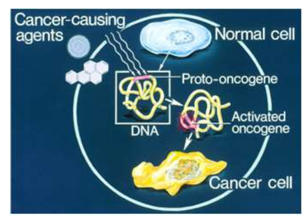
Oncogenes

Gene that has a potential to cause cancer

- Mutation and or environmental influence (epigenetic modification) can cause the gene to be activated
- Epigenetic modification of oncogenes often happens when there is methylation dysfunction



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Proto-onco genes

Proto-oncogenes are normal genes involved in controlling cell growth and division. They regulate processes like cell proliferation, differentiation, and apoptosis (programmed cell death). Think of them like the gas pedal in a car, promoting normal cell growth when needed.

When a proto-oncogene undergoes a mutation or is expressed abnormally, it can be transformed into an oncogene. This conversion can happen through various mechanisms like point mutations, chromosomal translocations, or gene amplifications.

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Proto-onco genes

Once activated, oncogenes can promote uncontrolled cell growth and division, leading to the formation of tumors and the development of cancer. Oncogenes, in essence, are like a faulty accelerator that's stuck in the "on" position, constantly telling cells to divide and multiply, according to the National Human Genome Research Institute (NHGRI).

Most oncogene mutations are acquired during a person's lifetime, rather than being inherited. They can arise from random DNA replication errors or be caused by environmental factors like carcinogens or radiation.

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Oncogenes and Tumor Suppressor Genes

Oncogenes are like the gas pedal in a car: They promote cell growth and division.

Tumor suppressor genes are like the brakes: They regulate and slow down cell division or initiate programmed cell death (apoptosis) if a cell is damaged.

Tumor suppressor genes encode proteins that regulate and slow down the cell cycle, ensuring normal cell growth and division. They can also trigger apoptosis if the cell is severely damaged.

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Tumor Suppressor Genes

Tumor suppressor genes become problematic when they are inactivated or lose their function due to mutations. This inactivation can be compared to faulty brakes in a car – they don't work properly to stop or slow down the car, leading to uncontrolled movement.

Effect: When tumor suppressor genes are inactivated, cells lose the ability to regulate growth and division, allowing them to multiply uncontrollably and potentially form tumors.

Examples: The TP53 gene is a well-known example, involved in cell cycle control, DNA repair, and apoptosis, says the National Cancer Institute. BRCA1 and BRCA2 genes, involved in DNA repair and cell death, are linked to an increased risk of breast and ovarian cancer when mutated.

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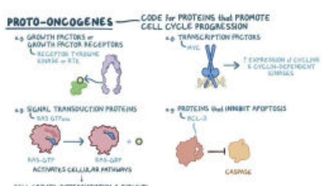
Oncogenes and Tumor Suppressor Genes

The balance between the activity of oncogenes and tumor suppressor genes is critical for maintaining normal cell growth and preventing cancer. Oncogenes push cells to divide, while tumor suppressor genes put the brakes on. When this delicate balance is disrupted by mutations that activate oncogenes or inactivate tumor suppressor genes, the risk of cancer increases significantly



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Caretaker Genes/Stability Genes

Create "stability" in the genome. Sometimes termed suppressor genes.

- nucleotide excision repair
- base excision repair
- non-homologous end joining recombination pathways
- mismatch repair pathways
- telomere metabolism.

Example: BRCA1, BRCA2

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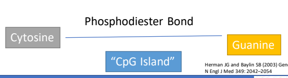
DNA

DNA is made up of four nucleotide bases: Adenine, Thymidine, Cytosine, and Guanine

In mammalian DNA, 5-methylcytosine is found in approximately 4% of genomic DNA, primarily at cytosine–guanosine dinucleotides (CpGs). Such CpG sites occur at lower than expected frequencies throughout the human genome but are found more frequently at small stretches of DNA called CpG islands. Nature Clinical Practice Oncology (2005) 2, S4-S11

CpG islands- located at the 5' region; where most of the promoter region is located



Herman JG and Baylin SB (2003) Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med 349: 2042–2054

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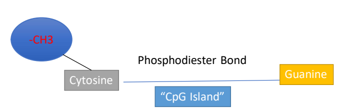
DNA-Methylation

Methylation- addition of CH3 to cytosine (C) at CpG Islands

Methylation blocks the binding of transcriptional proteins

- Genes are inactivated or silenced

In contrast to the bulk of genomic DNA, in which most CpG sites are heavily methylated, CpG islands in germ-line tissue and promoters of normal somatic cells remain unmethylated, allowing gene expression to occur.



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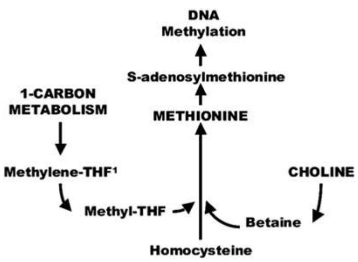
DNA Methylation



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DNA Methylation

"DNA methylation helps to maintain **transcriptional silence** in nonexpressed or noncoding regions of the genome. For example, pericentromeric HETEROCHROMATIN, which is condensed and transcriptionally inactive, is heavily methylated. Hypermethylation thus ensures this DNA is late-replicating and transcriptionally quiescent, and suppresses the expression of any potentially harmful viral sequences or transposons that may have integrated into such sites containing highly repetitive sequences."

Bestor TH (2000) The DNA methyltransferases of mammals. Hum Mol Genet 9: 2395–2402
Bird A (2002) DNA methylation patterns and epigenetic memory. Genes Dev 16: 6–21
Jones PA and Baylin SB (2002) The fundamental role of epigenetic events in cancer. Nat Rev Genet 3: 415–428

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Cancer and DNA Methylation

DNA methylation plays a significant role in cancer development and progression. It is an epigenetic modification where a methyl group is added to DNA, affecting gene expression. While DNA methylation is a normal process, aberrant methylation patterns are frequently observed in cancer cells, both hypermethylation (excessive) and hypomethylation (reduced). These changes can silence tumor suppressor genes, promote genomic instability, and contribute to metastasis.

Hypermethylation: Hypermethylation of CpG islands (regions of DNA with high CpG content) in promoter regions of tumor suppressor genes can lead to their silencing, effectively turning off the genes that normally prevent tumor growth.

Hypomethylation: Global hypomethylation (reduced methylation across the genome) can also contribute to cancer by increasing genomic instability and activating oncogenes (genes that promote cell growth).

Mismatch Repair Genes: Aberrant methylation of mismatch repair (MMR) genes can lead to deficiencies in DNA repair, resulting in microsatellite instability (MSI), a hallmark of some cancers.

Epithelial-Mesenchymal Transition (EMT): DNA methylation can contribute to the EMT process, a crucial step in metastasis, by affecting the expression of genes like E-cadherin, a protein that helps cells adhere to each other.

Metastasis: Studies show that specific DNA methylation patterns are associated with metastasis in various cancers, and these patterns can be used as potential prognostic markers.

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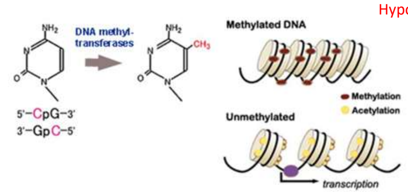
DNA Methylation

Aging Cells Result in Hypomethylation



Aging cells: Body wide 5-methyl-cystosine reduction (hypomethylation)

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Its not all about HYPO-methylation

Hyper-methylation can cause suppression of tumor suppressor genes and can trigger oncogenesis
- Chromosomal instability
- Sporadic gene expression

Currently anti-methyl transferase drugs are being tested for their role in treating cancer

In cancer, EPIGENETIC SILENCING through methylation occurs at least as frequently as mutations or deletions and leads to aberrant silencing of normal tumor-suppressor function. Nat Rev Genet. 2002 Jun;3(6):415-28

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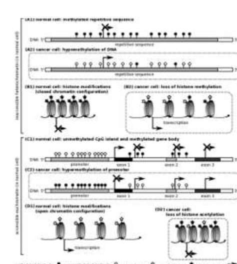
Cancer Epigenetics

CpG site- promoter region
- Hypomethylation of these region of genetic code led to overexpression of oncogenes

Hypermethylation of CpG islands affects genes involved in cell cycle control, DNA repair, cell adhesion, signal transduction, apoptosis and cell differentiation. In tumour cells, local promoter hypermethylation is often accompanied [preceded] by global **hypomethylation**."



Holm k, Hegardt C et al. Molecular subtypes of breast cancer are associated with characteristic DNA methylation patterns. Breast Cancer Res 2010;12(3):R36.

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Hypo or Hyper Methylation


DNA methylation in cancer: too much, but also too little

Melanie Ehrlich

- DNA hypomethylation in cancer often affects more of the genome than does hypermethylation so that net losses of genomic 5-methylcytosine (m5C) are seen in many human cancers Gama-Sosa et al., 1983b.

Hypo	Hyper of CpG
Colon adenocarcinoma	Colon Cancer
Ovarian tumors	Some breast cancers
Hepatocellular carcinoma	Kidney
Prostatic metastasis	Bladder
Lymphocytic leukemia	Esophageal
Highly dysplastic cervical tissue	Pancreatic
	Liver Cancers

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Hypo or Hyper Methylation


DNA methylation in cancer: too much, but also too little

Melanie Ehrlich

- Hypermethylation silences tumor suppressor genes
- Hypomethylation promotes cancer progression by allowed increased gene transcription

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Is timing everything?

Published in final edited form as:
Cancer Prev Res (Phila). 2012 July ; 5(7): 911–920. doi:10.1158/1940-6207.CAPR-11-0544.

Dietary Methyl Donor Depletion Protects Against Intestinal Tumorigenesis in $Apc^{Min/+}$ Mice

Study Objective: This study examines the effects of folate deficiency, in combination with choline, methionine and vitamin B12 depletion, on intestinal tumorigenesis in ApcMin/+ mice.

Methyl donor sufficient (MDS) and deficient (MDD) diets were started at 5 or 10 weeks of age and tumors evaluated at 16 weeks.

MDD suppressed intestinal tumor formation in ApcMin/+ mice (~80%) when started at 5 weeks of age. The protective effect was lost when MDD was initiated at 10 weeks of age, **indicating an important time-dependency on cancer suppression.**

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In Conclusion: 3 Causes of Cancer

1) Chromosome Alteration: Errors in DNA replication and repair. Environmental factors, toxins, chemicals, radiation etc.

2) Mutations (spelling mistakes): alterations in an organism's DNA sequence, which can affect how genes are expressed and potentially lead to changes in traits or even diseases.

3) Methylation issues: Widespread epigenetic changes, including global hypomethylation (overall loss of methylation) that causes genome instability, and focal hypermethylation (excess methylation) at gene promoters that silences tumor suppressor genes, preventing their normal function in cell growth control

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