REPORT ON CANCER VISION

REPORT

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What Is Cancer?

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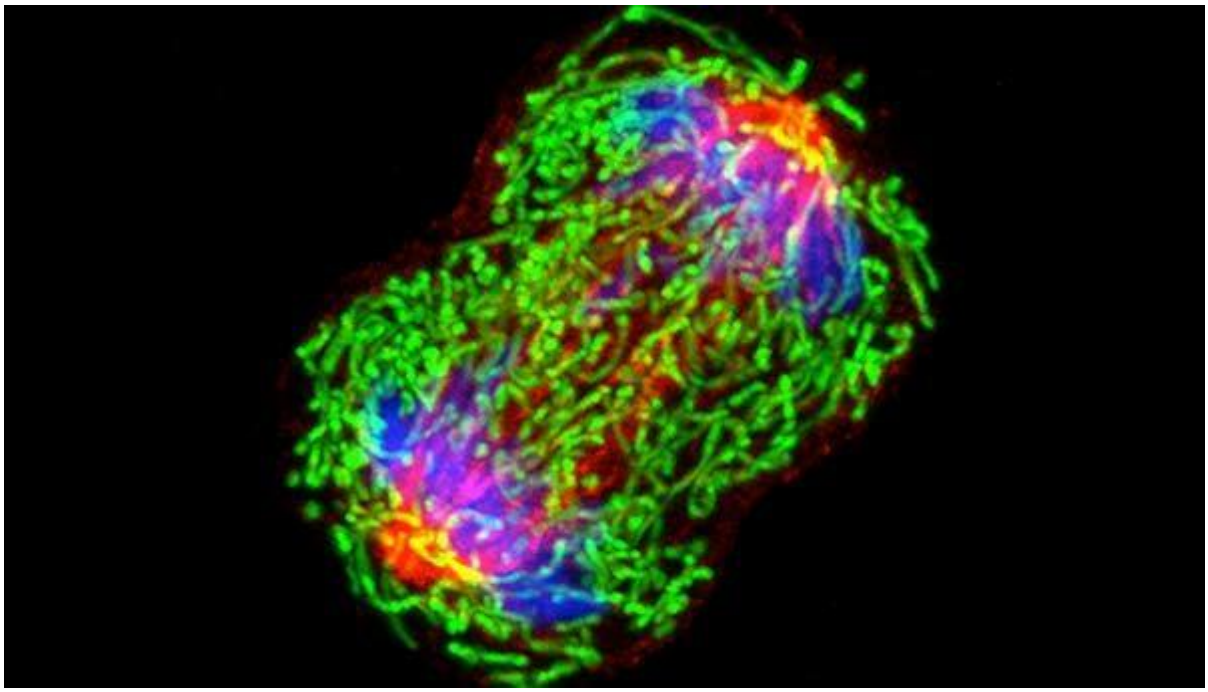
ON THIS REPORT:

- The Definition of Cancer
- Differences between Cancer Cells and Normal Cells
- How Does Cancer Develop?
- Types of Genes that Cause Cancer
- When Cancer Spreads
- Tissue Changes that Are Not Cancer
- Types of Cancer



A dividing breast cancer cell.

Credit: National Cancer Institute / Univ. of Pittsburgh Cancer Institute

The Definition of Cancer

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.

Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.

Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous (benign).

Cancerous tumors spread into, or invade, nearby tissues and can travel to distant places in the body to form new tumors (a process called metastasis). Cancerous tumors may also be called malignant tumors. Many cancers form solid tumors, but cancers of the blood, such as leukemias, generally do not.

Benign tumors do not spread into, or invade, nearby tissues. When removed, benign tumors usually don't grow back, whereas cancerous tumors sometimes do. Benign tumors can sometimes be quite large, however. Some can cause serious symptoms or be life threatening, such as benign tumors in the brain.

Differences between Cancer Cells and Normal Cells

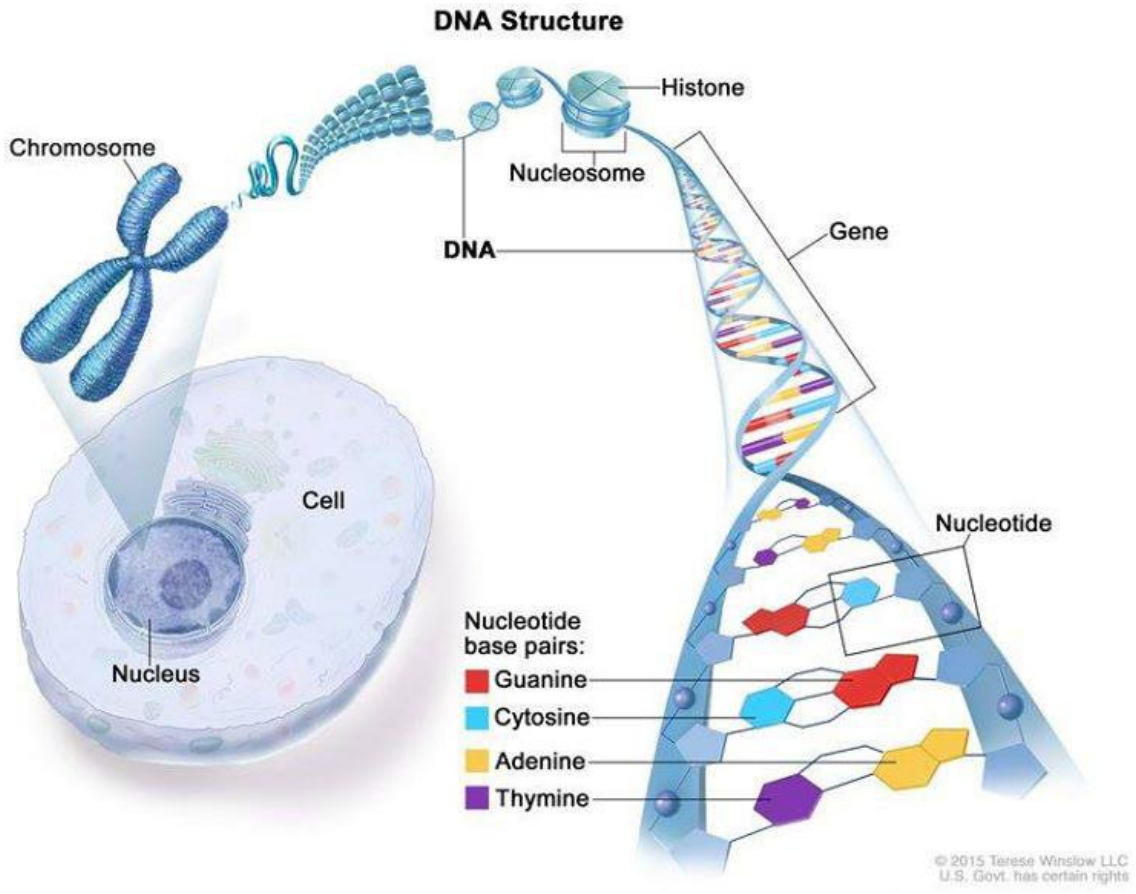
Cancer cells differ from normal cells in many ways. For instance, cancer cells:

- grow in the absence of signals telling them to grow. Normal cells only grow when they receive such signals.
- ignore signals that normally tell cells to stop dividing or to die (a process known as programmed cell death, or apoptosis).
- invade into nearby areas and spread to other areas of the body. Normal cells stop growing when they encounter other cells, and most normal cells do not move around the body.
- tell blood vessels to grow toward tumors. These blood vessels supply tumors with oxygen and nutrients and remove waste products from tumors.
- hide from the immune system. The immune system normally eliminates damaged or abnormal cells.
- trick the immune system into helping cancer cells stay alive and grow. For instance, some cancer cells convince immune cells to protect the tumor instead of attacking it.
- accumulate multiple changes in their chromosomes, such as duplications and deletions of chromosome parts. Some cancer cells have double the normal number of chromosomes.
- rely on different kinds of nutrients than normal cells. In addition, some cancer cells make energy from nutrients in a

different way than most normal cells. This lets cancer cells grow more quickly.

Many times, cancer cells rely so heavily on these abnormal behaviors that they can't survive without them. Researchers have taken advantage of this fact, developing therapies that target the abnormal features of cancer cells. For example, some cancer therapies prevent blood vessels from growing toward tumors, essentially starving the tumor of needed nutrients.

How Does Cancer Develop?



Cancer is caused by certain changes to genes, the basic physical units of inheritance. Genes are arranged in long strands of tightly packed DNA called chromosomes.
Credit: © Terese Winslow

Cancer is a genetic disease—that is, it is caused by changes to genes that control the way our cells function, especially how they grow and divide.

Genetic changes that cause cancer can happen because:

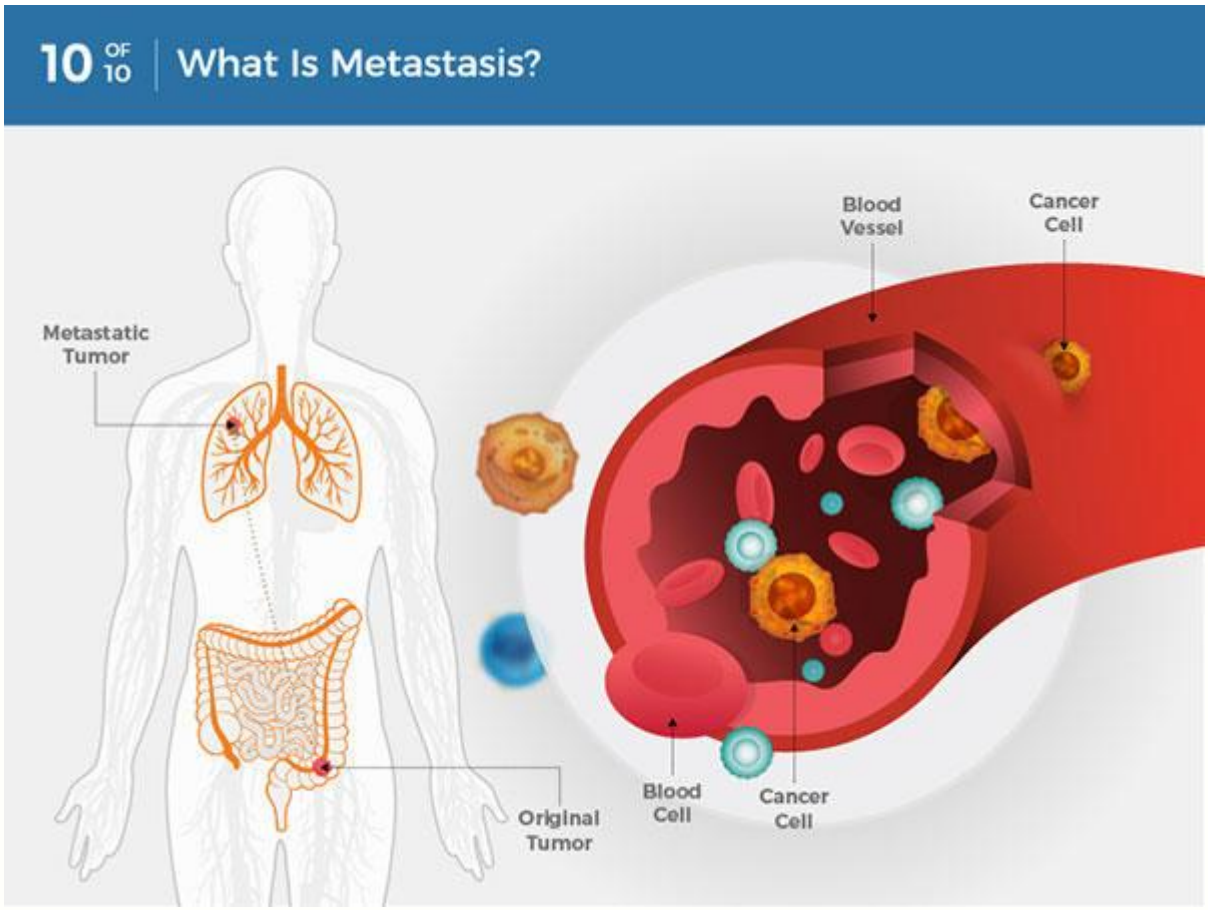
- of errors that occur as cells divide.
- of damage to DNA caused by harmful substances in the environment, such as the chemicals in tobacco smoke and ultraviolet rays from the sun. (Our Cancer Causes and Prevention section has more information.)
- they were inherited from our parents.

The body normally eliminates cells with damaged DNA before they turn cancerous. But the body's ability to do so goes down as we age. This is part of the reason why there is a higher risk of cancer later in life.

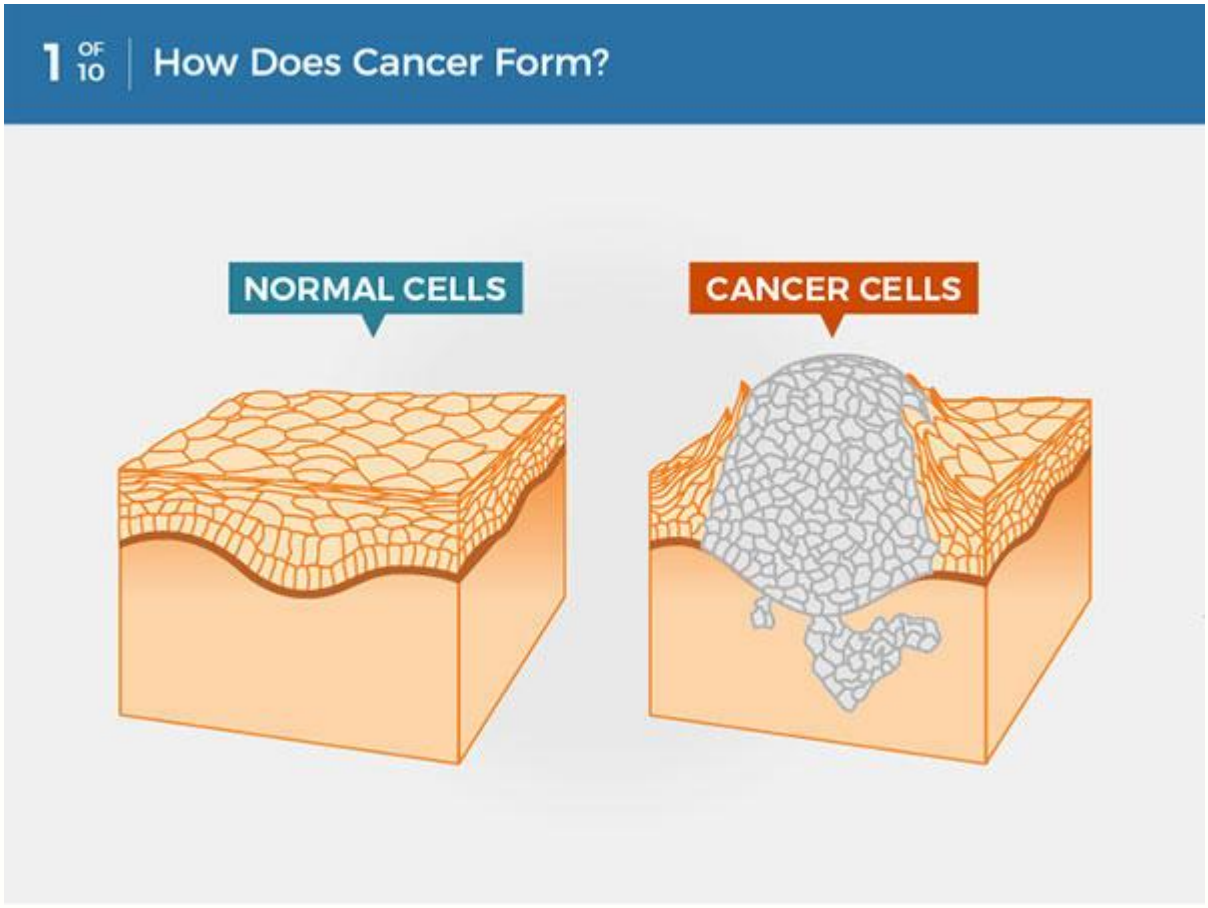
Each person's cancer has a unique combination of genetic changes. As the cancer continues to grow, additional changes will occur. Even within the same tumor, different cells may have different genetic changes.

Fundamentals of Cancer

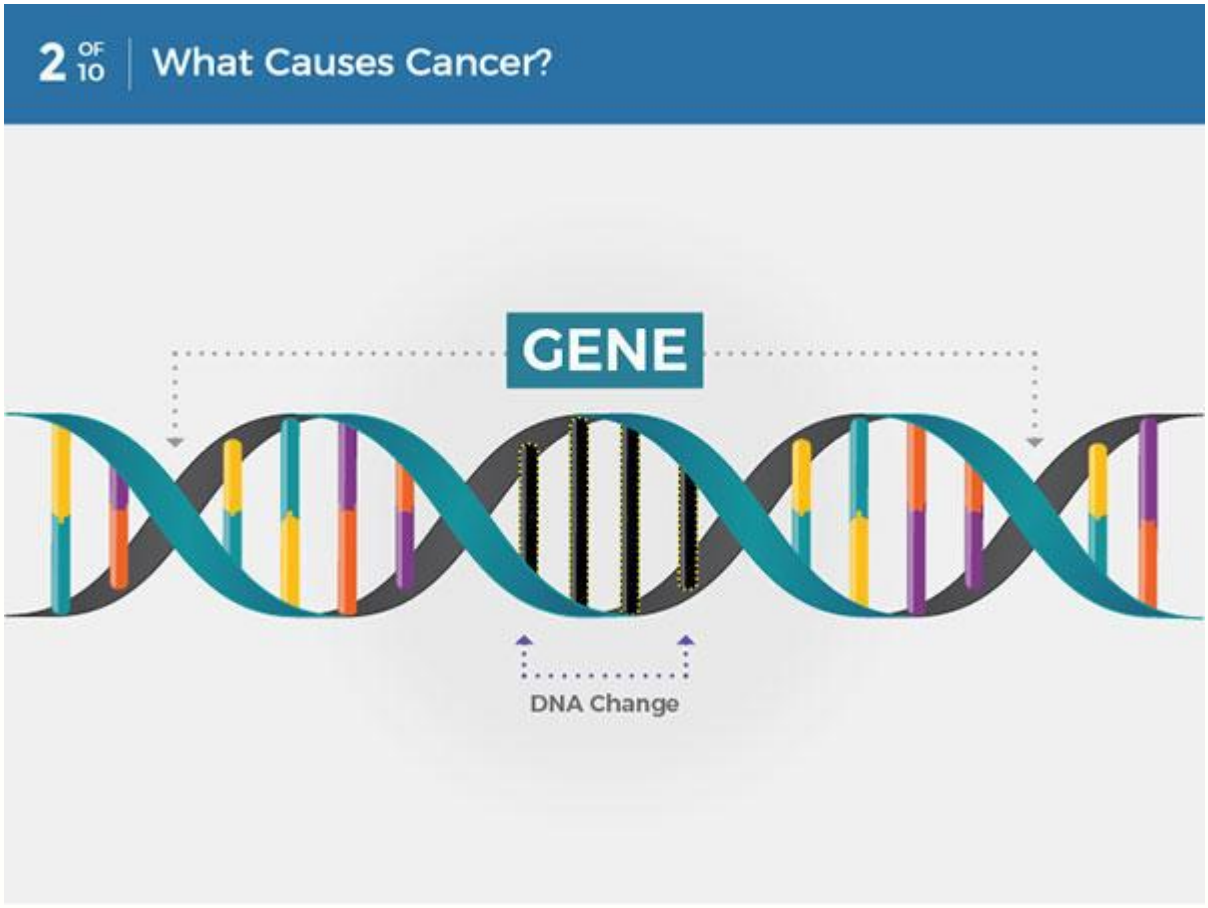
Previous



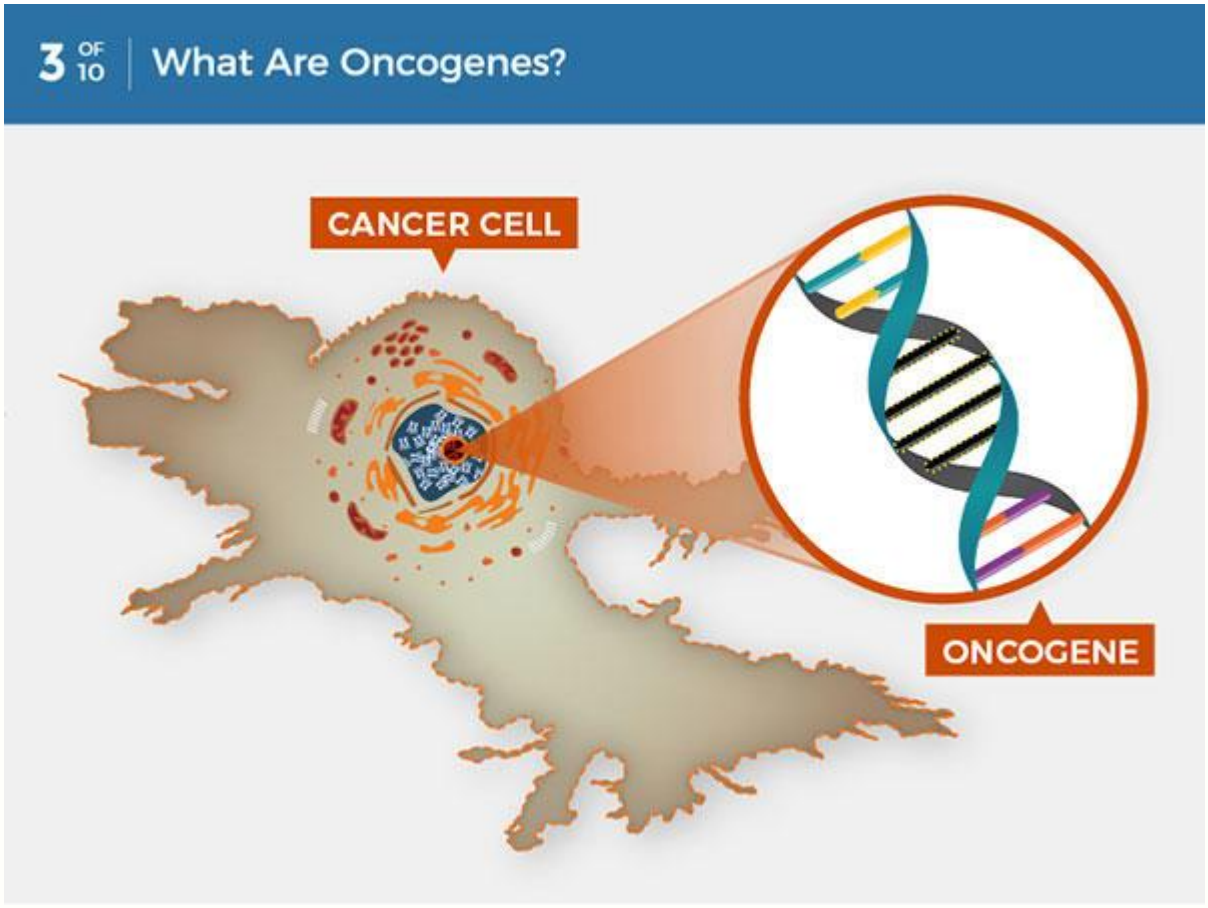
Cancer cells can break away from the original tumor and travel through the blood or lymph system to distant locations in the body, where they exit the vessels to form additional tumors. This is called metastasis.



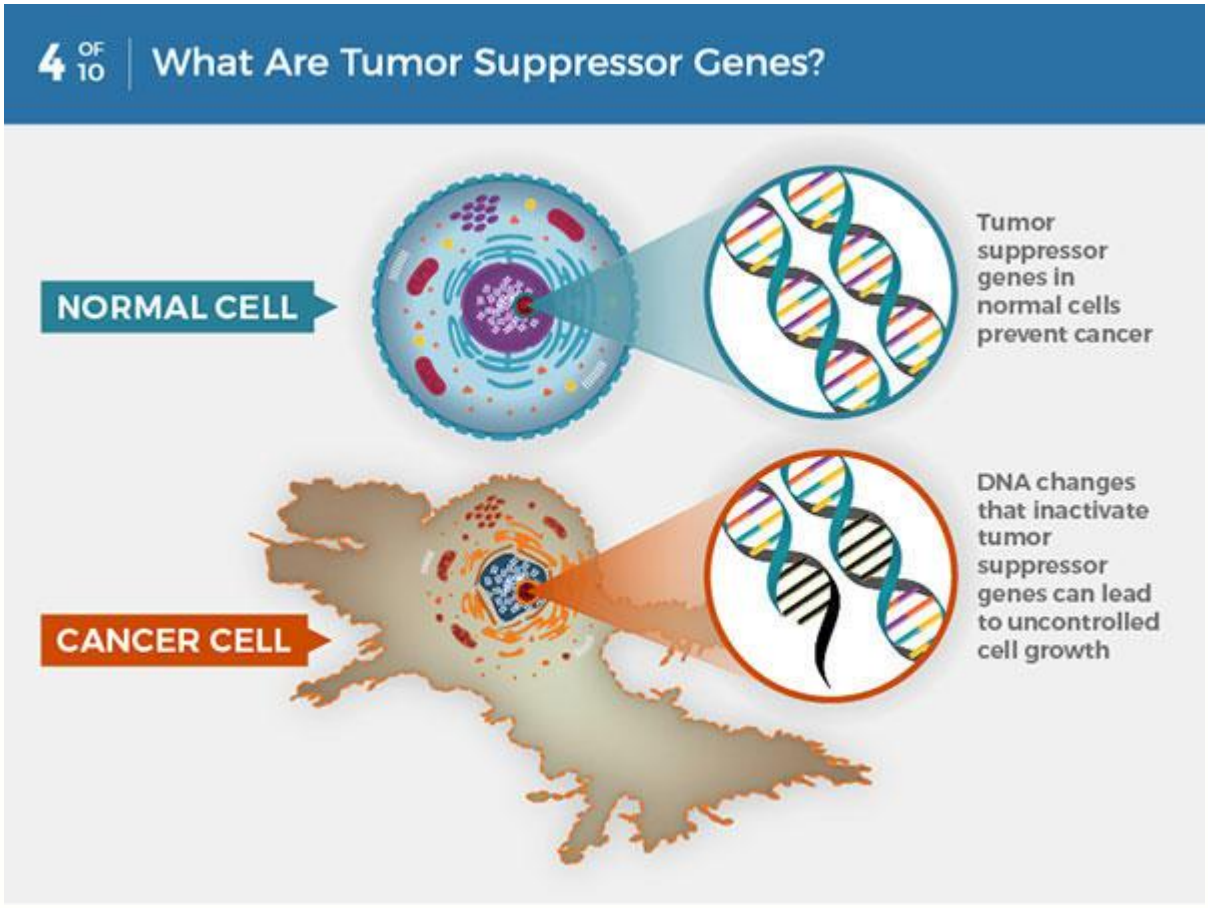
Cancer is a disease caused when cells divide uncontrollably and spread into surrounding tissues.



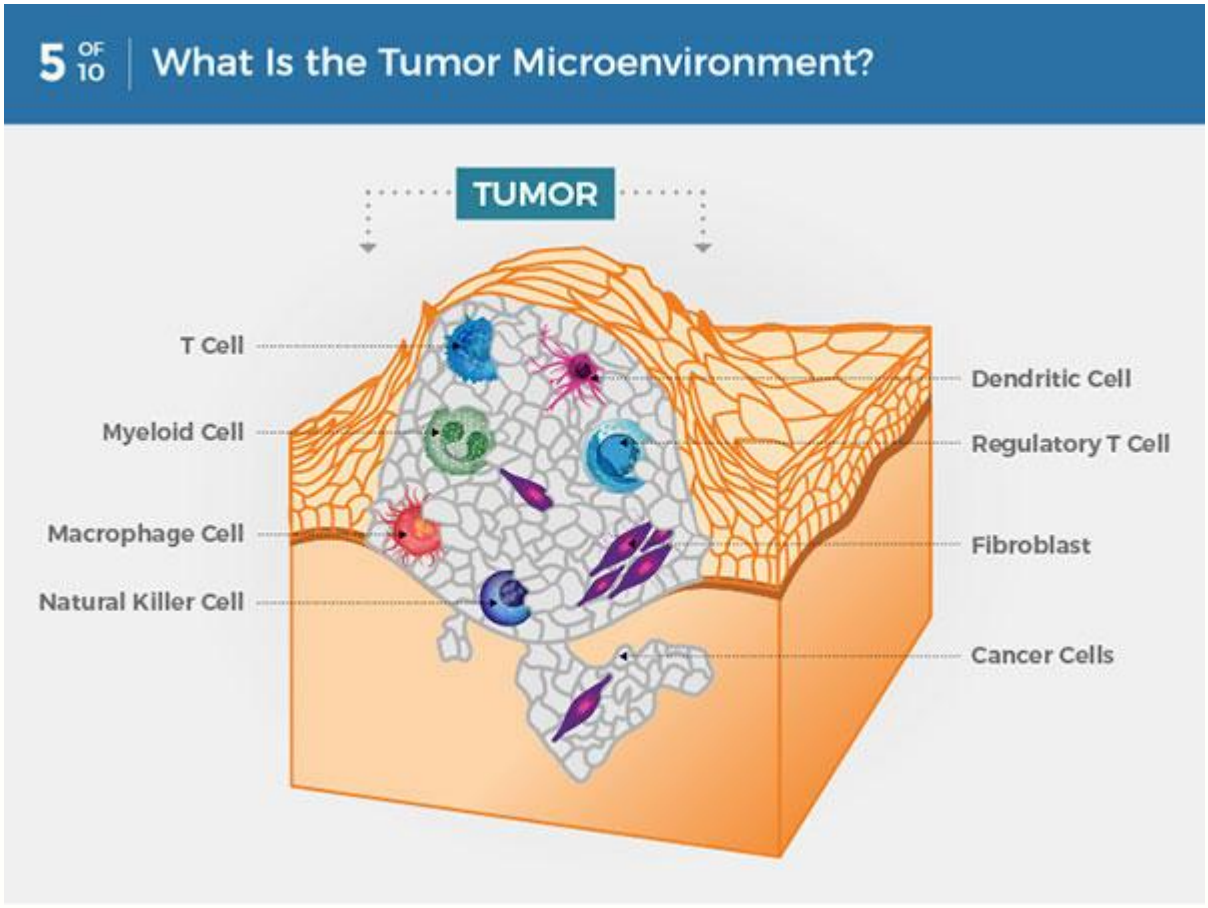
Cancer is caused by changes to DNA. Most cancer-causing DNA changes occur in sections of DNA called genes. These changes are also called genetic changes.



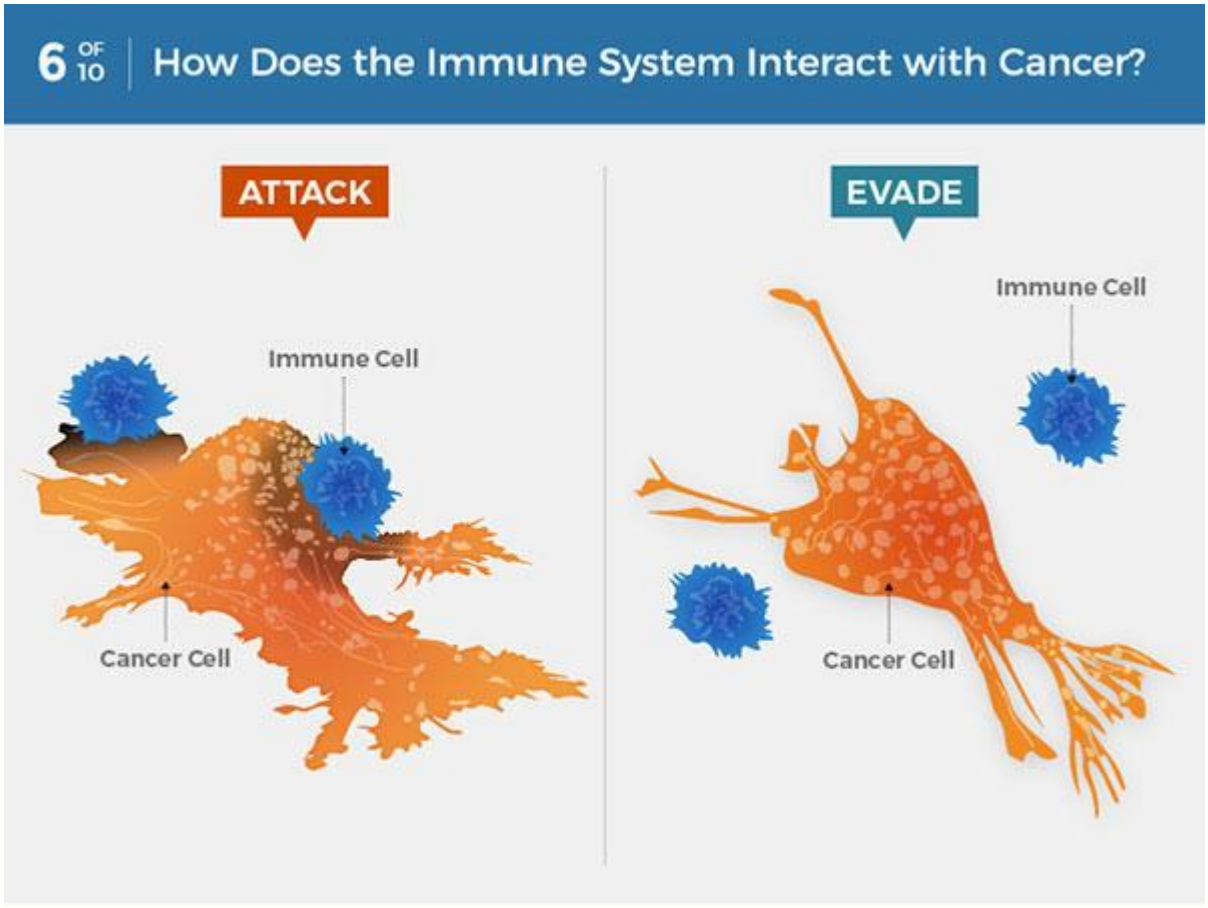
A DNA change can cause genes involved in normal cell growth to become oncogenes. Unlike normal genes, oncogenes cannot be turned off, so they cause uncontrolled cell growth.



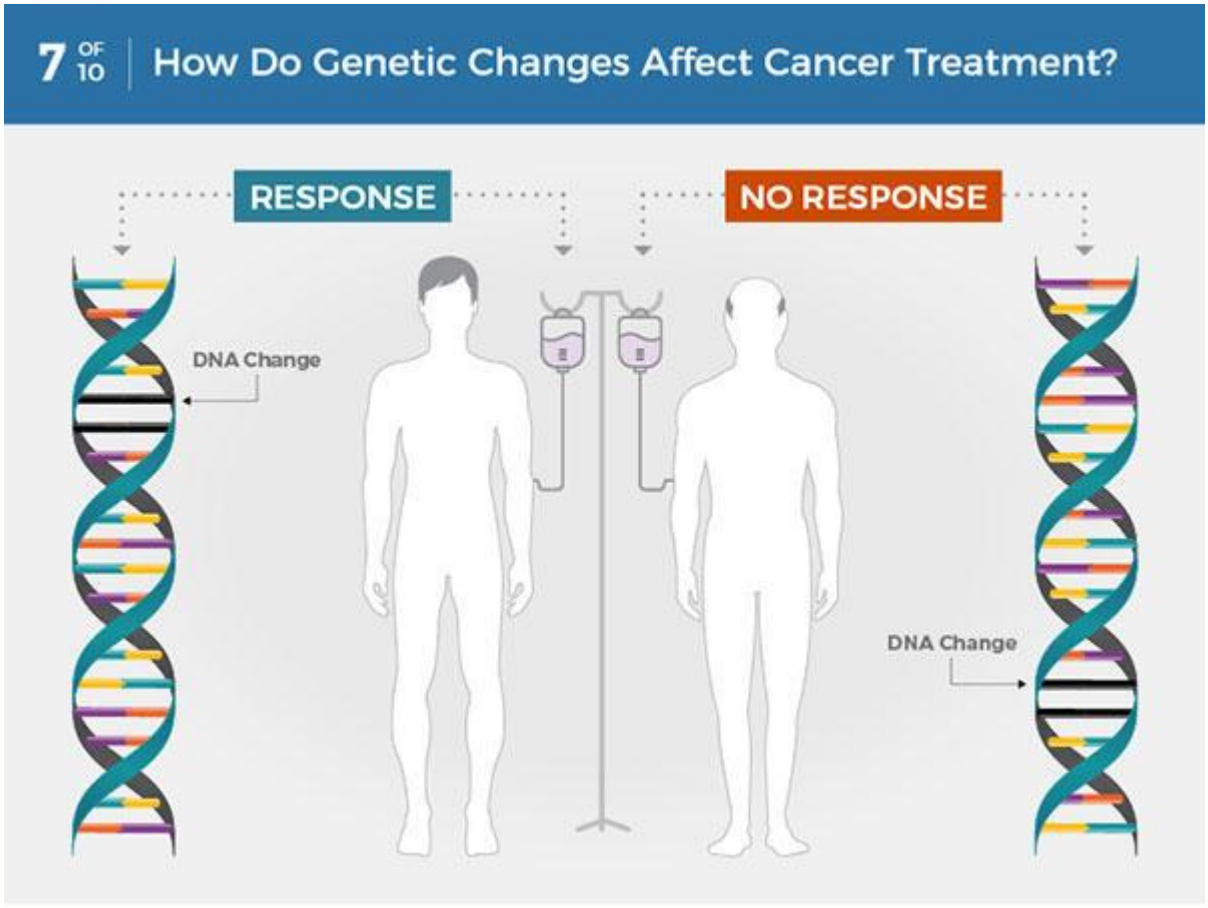
In normal cells, tumor suppressor genes prevent cancer by slowing or stopping cell growth. DNA changes that inactivate tumor suppressor genes can lead to uncontrolled cell growth and cancer.



Within a tumor, cancer cells are surrounded by a variety of immune cells, fibroblasts, molecules, and blood vessels—what's known as the tumor microenvironment. Cancer cells can change the microenvironment, which in turn can affect how cancer grows and spreads.



Immune system cells can detect and attack cancer cells. But some cancer cells can avoid detection or thwart an attack. Some cancer treatments can help the immune system better detect and kill cancer cells.



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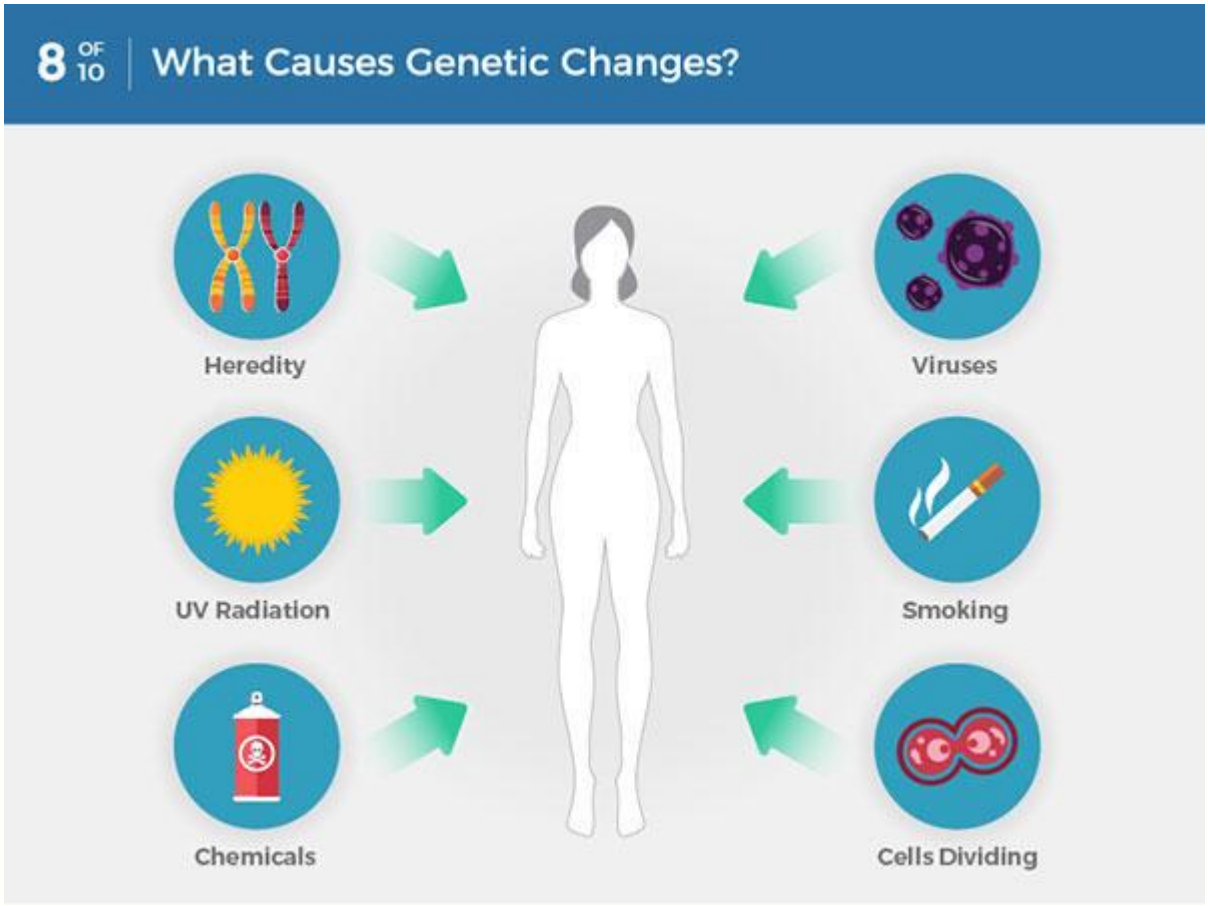
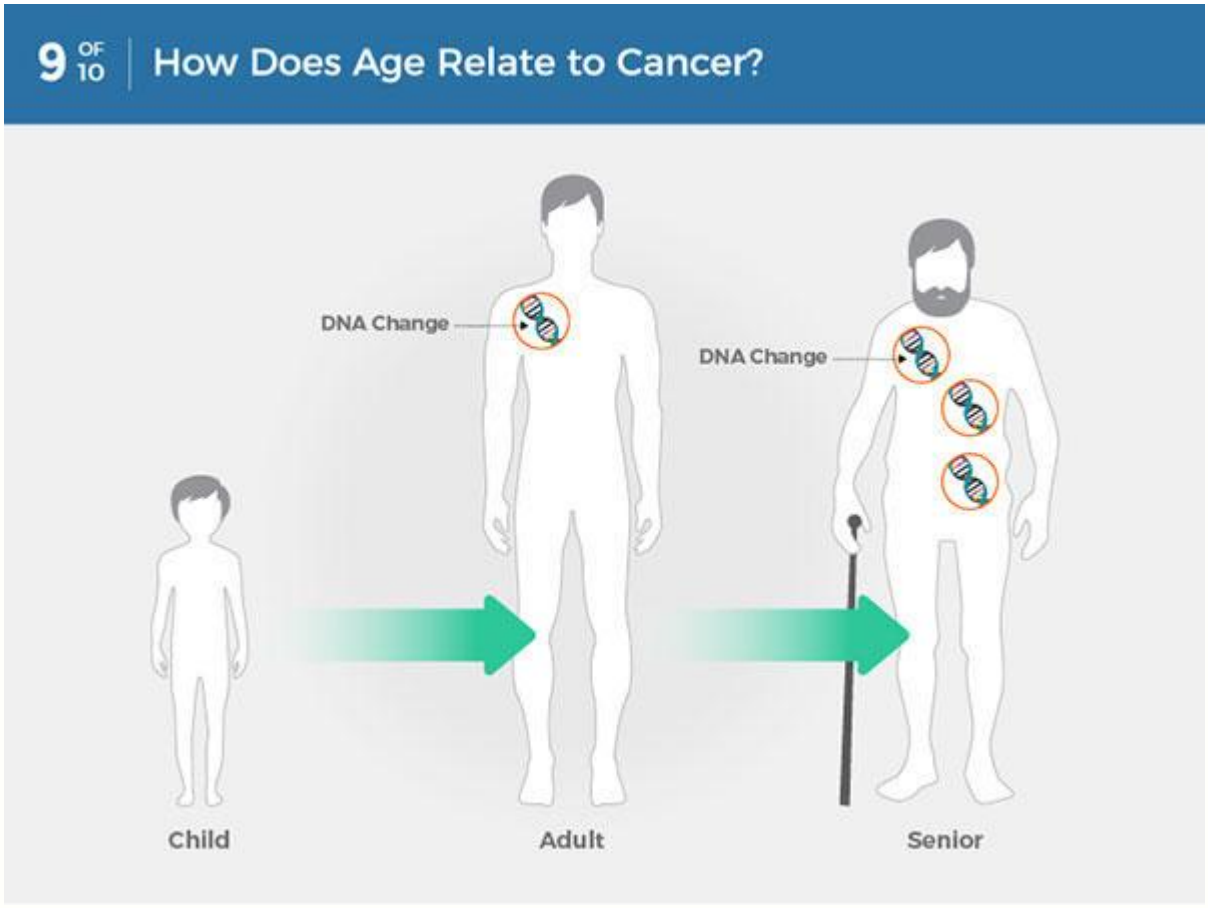
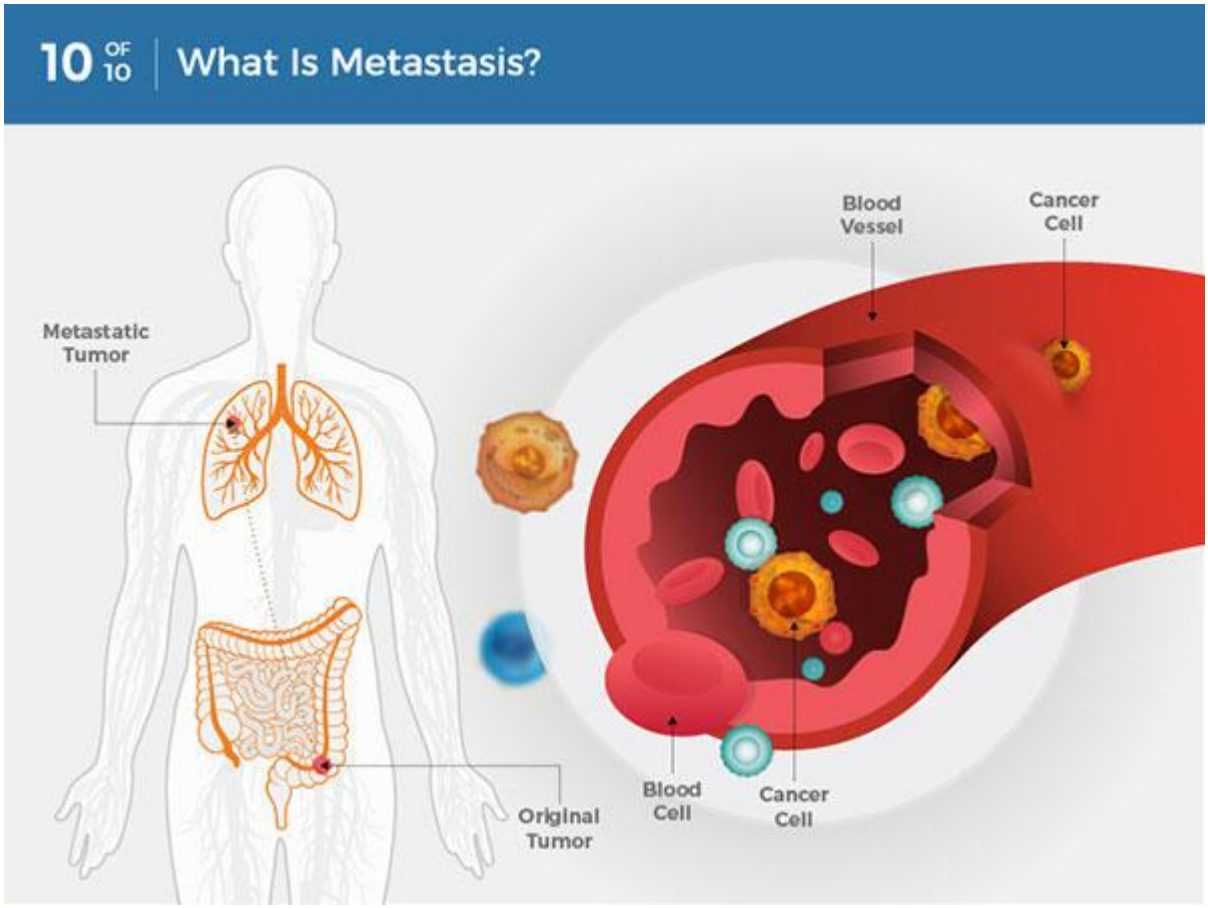


Credit: National Cancer Institute

Genetic changes that cause cancer can be inherited or arise from certain environmental exposures. Genetic changes can also happen because of errors that occur as cells divide.



Most often, cancer-causing genetic changes accumulate slowly as a person ages, leading to a higher risk of cancer later in life.



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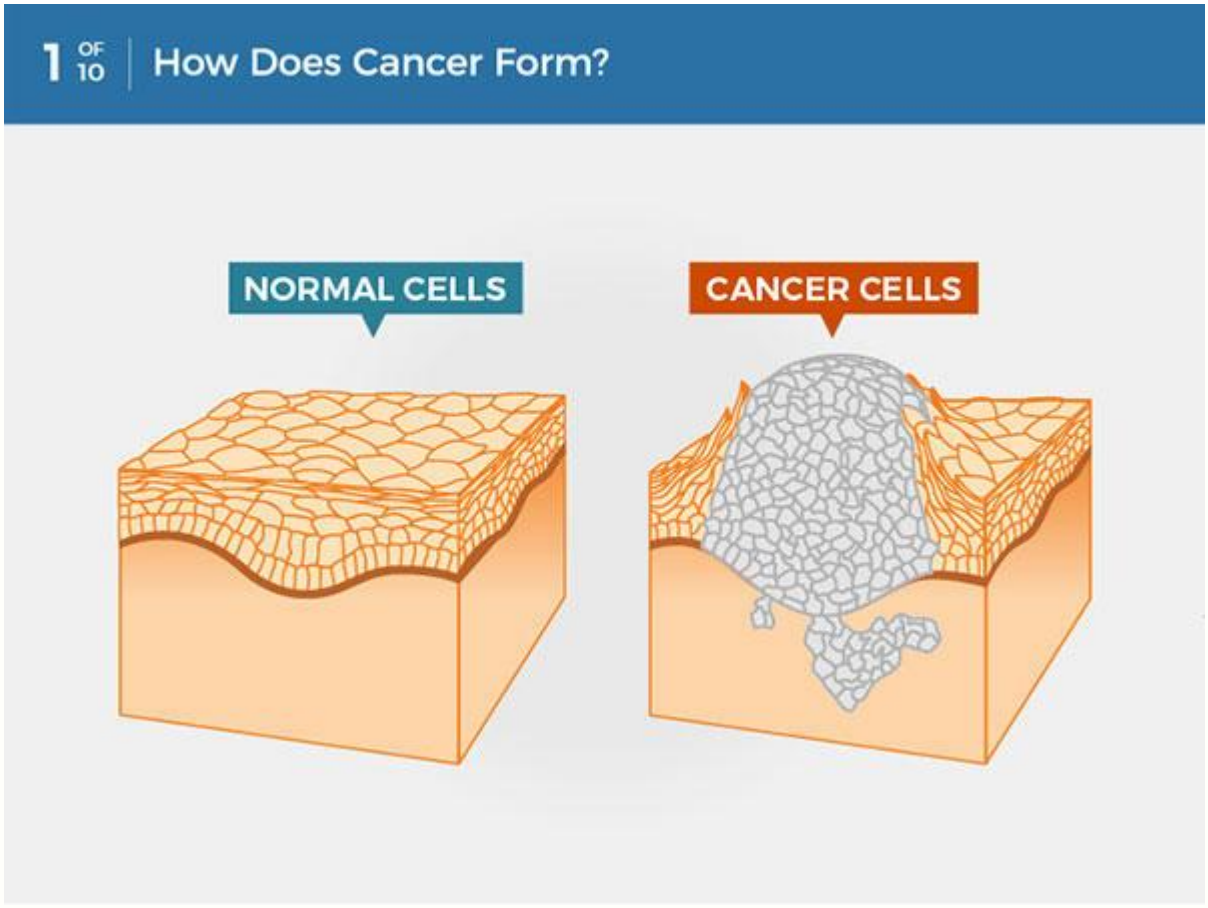

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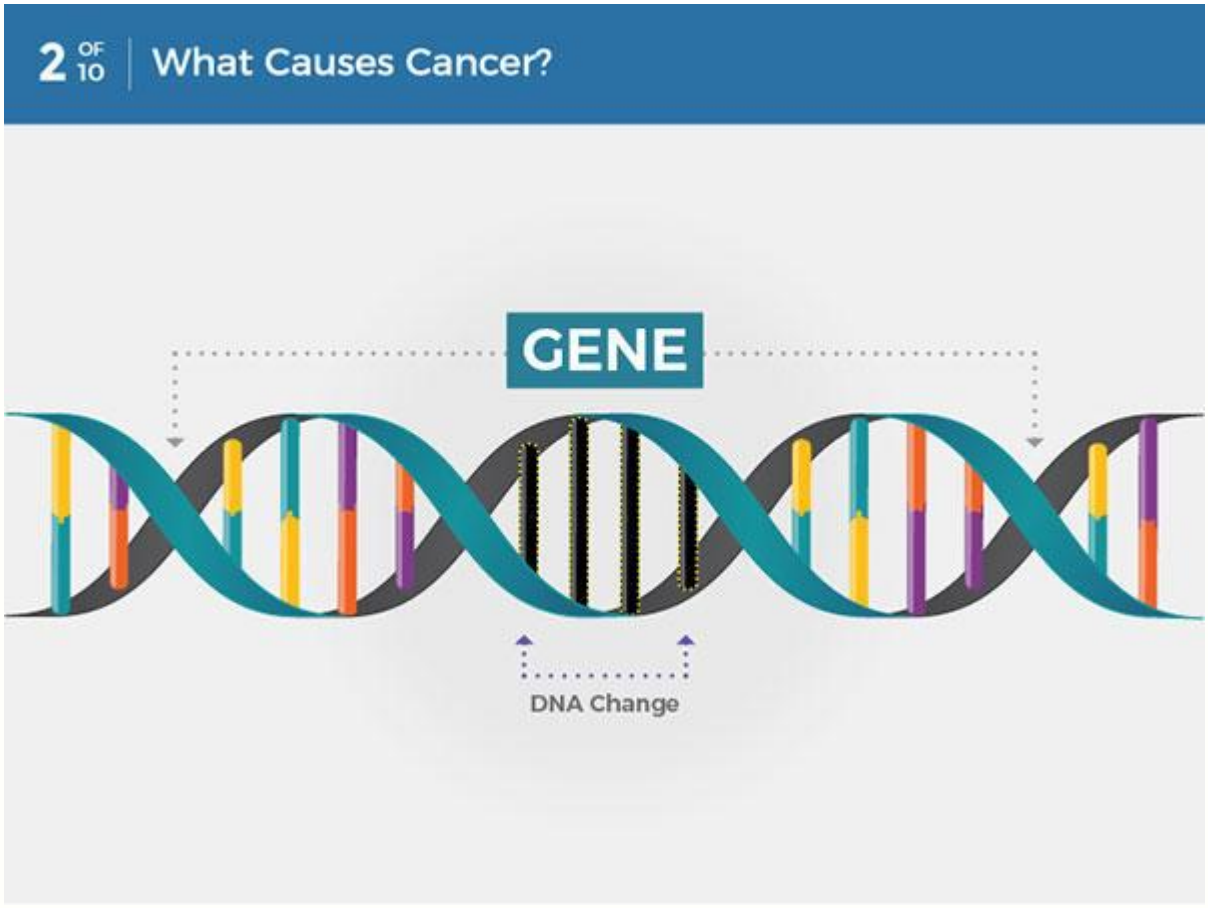

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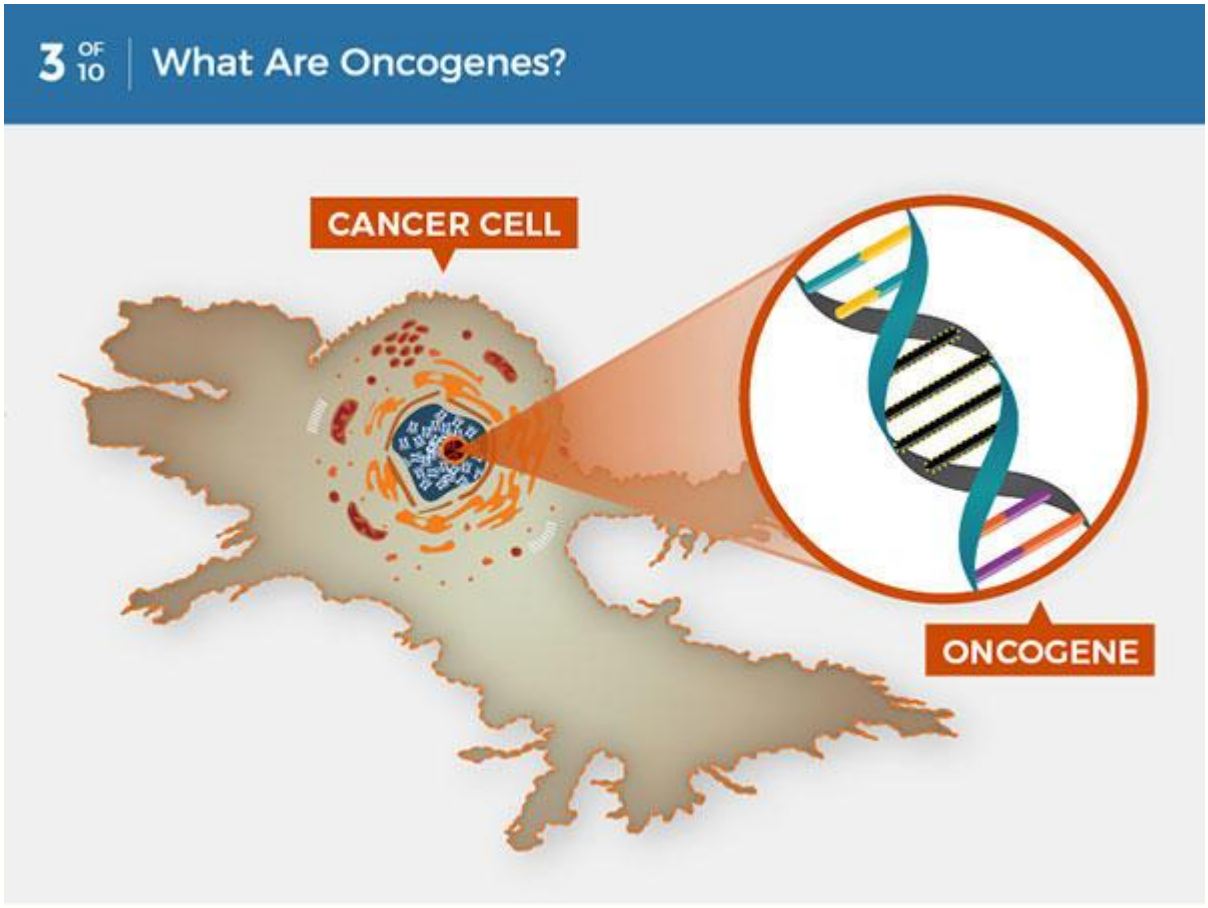

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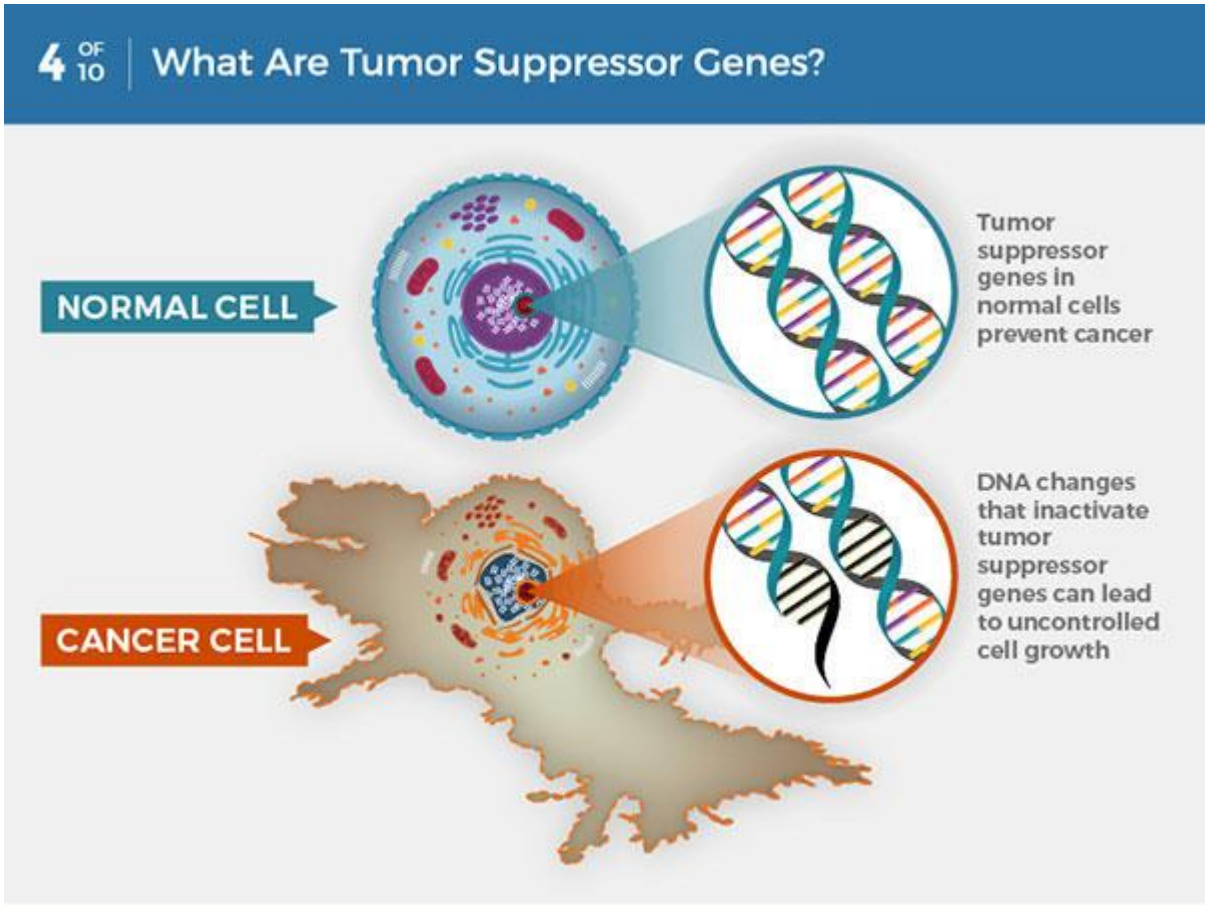

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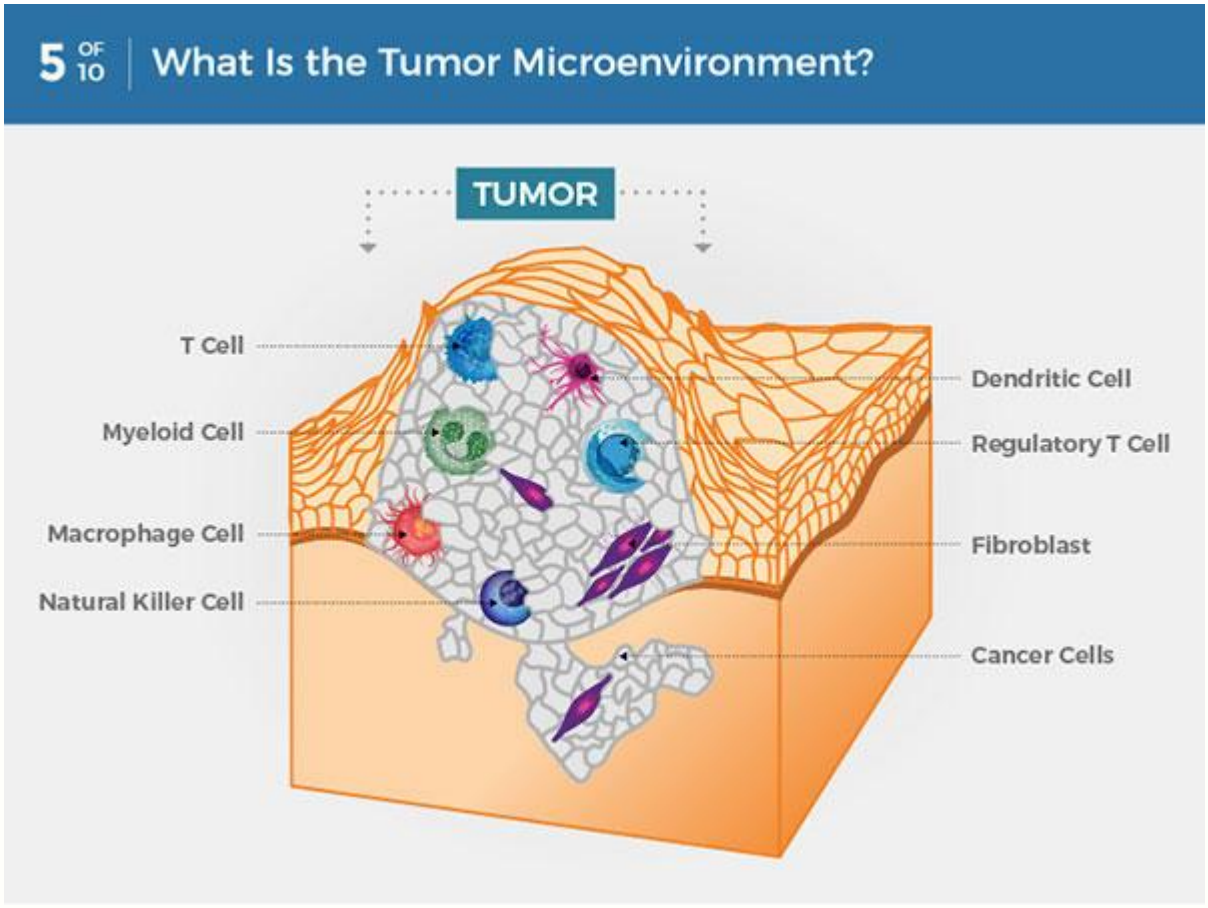

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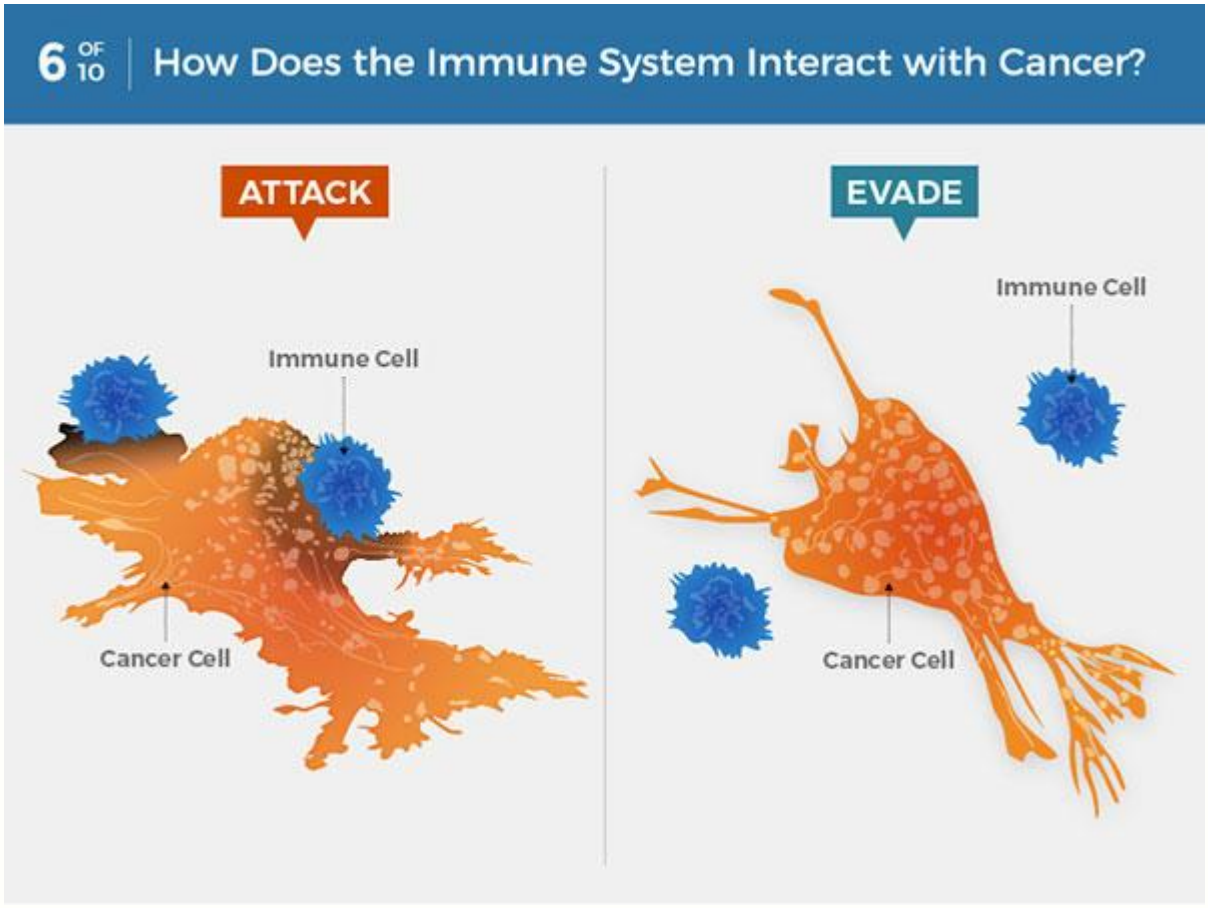

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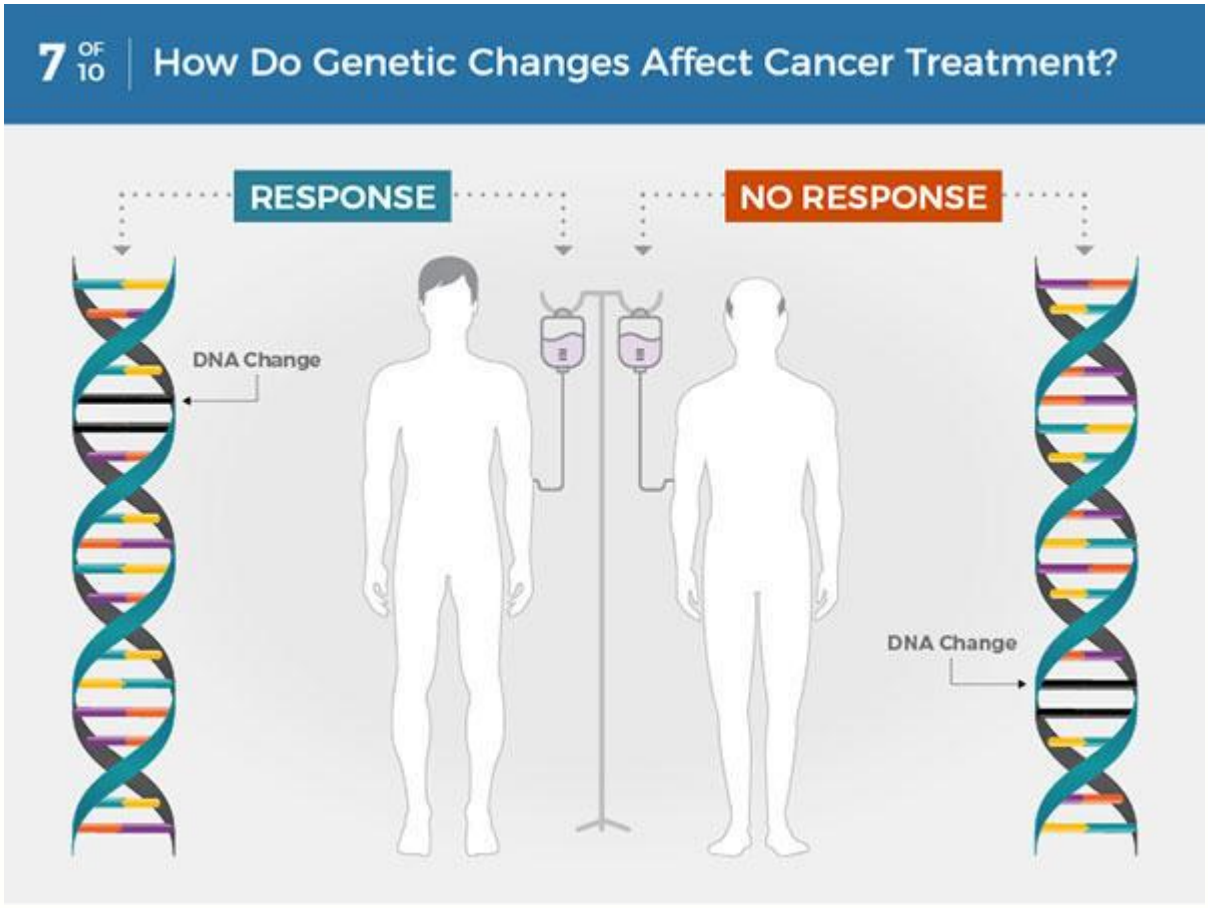

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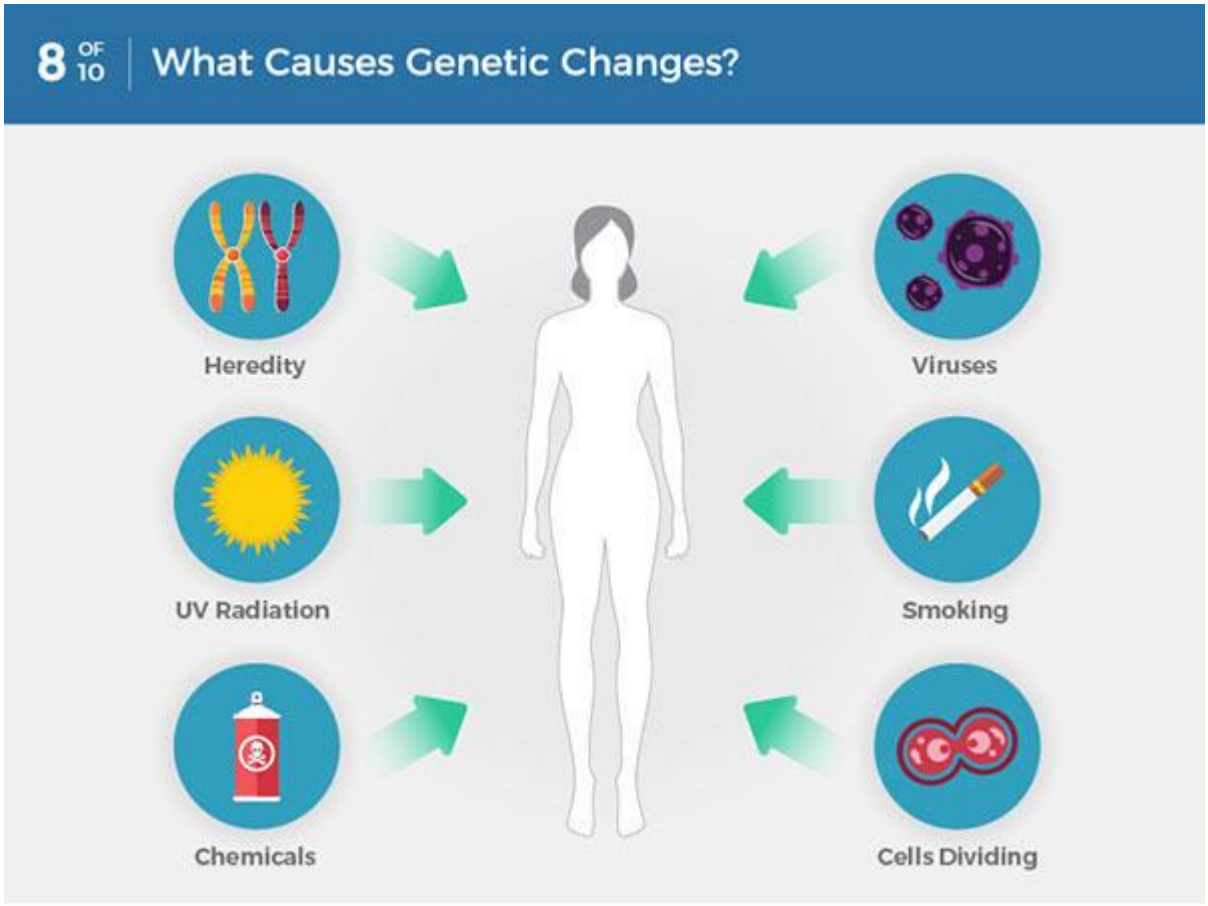

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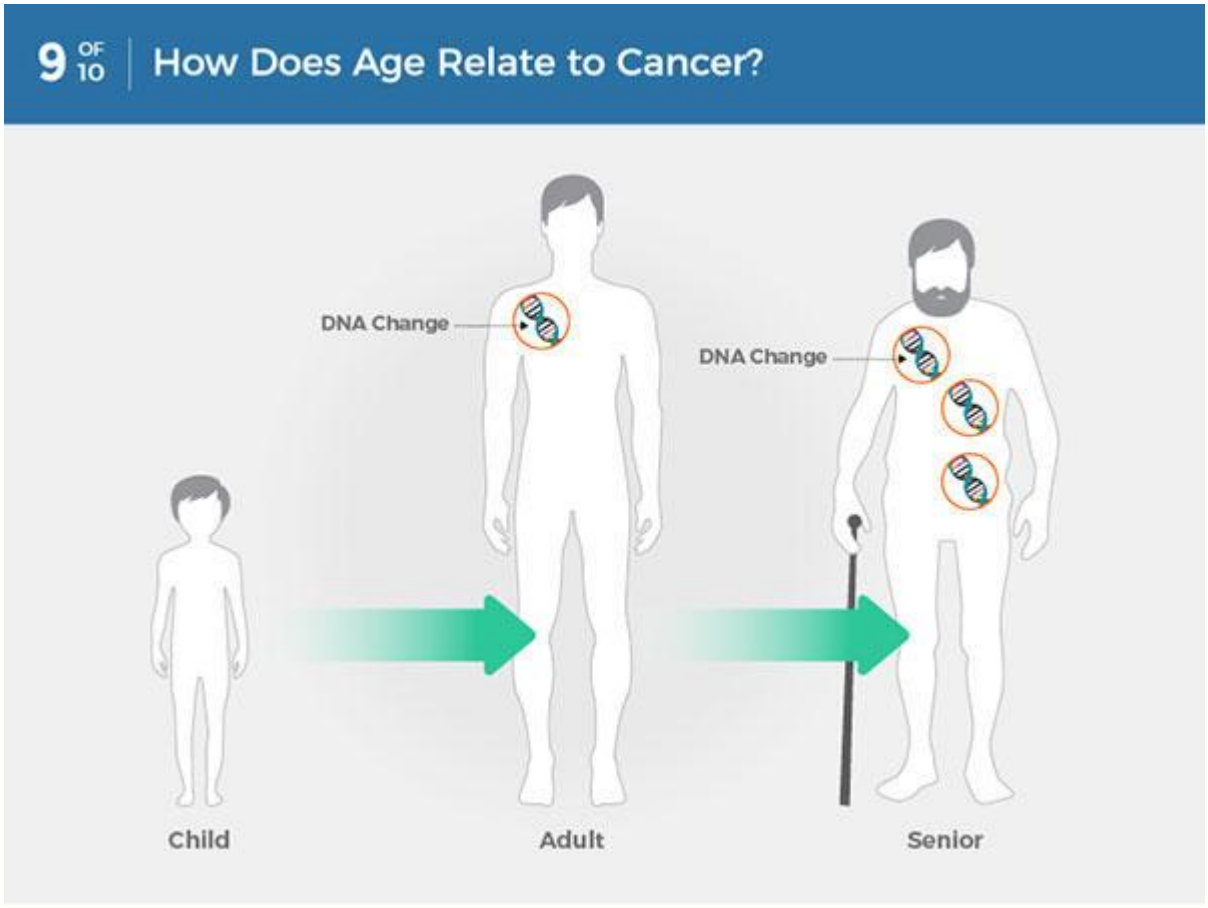

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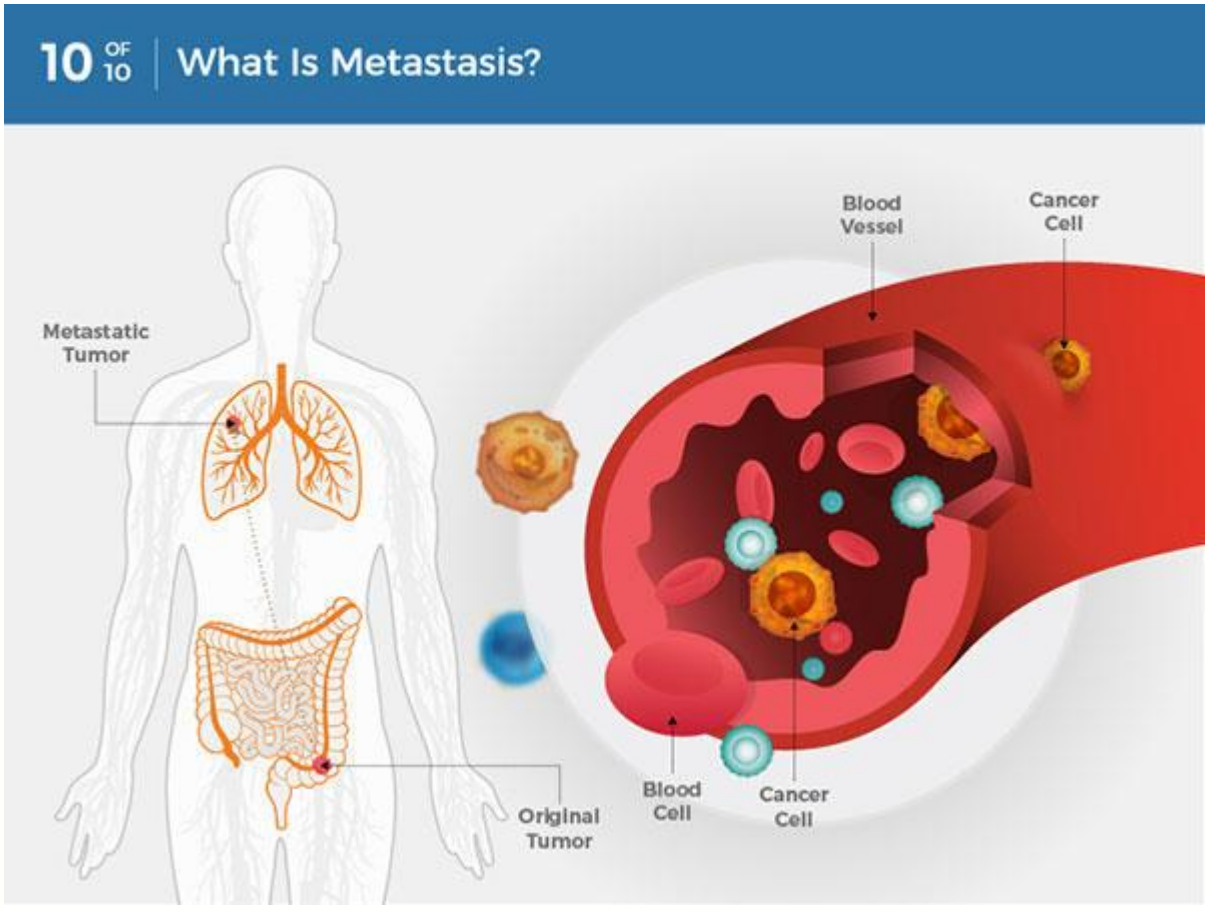

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Types of Genes that Cause Cancer

The genetic changes that contribute to cancer tend to affect three main types of genes—proto-oncogenes, tumor suppressor genes, and DNA repair genes. These changes are sometimes called "drivers" of cancer.

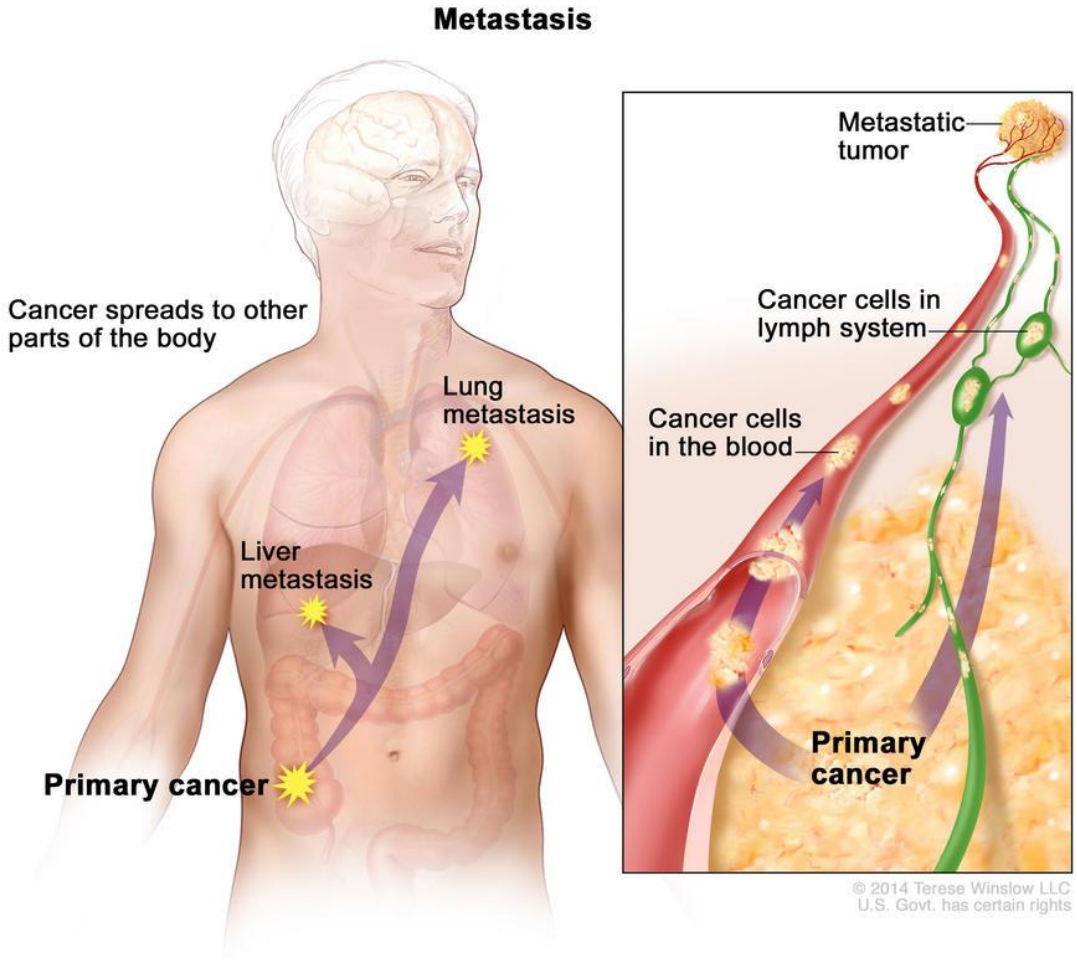
Proto-oncogenes are involved in normal cell growth and division. However, when these genes are altered in certain ways or are more active than normal, they may become cancer-causing genes (or oncogenes), allowing cells to grow and survive when they should not.

Tumor suppressor genes are also involved in controlling cell growth and division. Cells with certain alterations in tumor suppressor genes may divide in an uncontrolled manner.

DNA repair genes are involved in fixing damaged DNA. Cells with mutations in these genes tend to develop additional mutations in other genes and changes in their chromosomes, such as duplications and deletions of chromosome parts. Together, these mutations may cause the cells to become cancerous.

As scientists have learned more about the molecular changes that lead to cancer, they have found that certain mutations commonly occur in many types of cancer. Now there are many cancer treatments available that target gene mutations found in cancer. A few of these treatments can be used by anyone with a cancer that has the targeted mutation, no matter where the cancer started growing.

When Cancer Spreads



In metastasis, cancer cells break away from where they first formed and form new tumors in other parts of the body.
Credit: © Terese Winslow

A cancer that has spread from the place where it first formed to another place in the body is called metastatic cancer. The process by which cancer cells spread to other parts of the body is called metastasis.

Metastatic cancer has the same name and the same type of cancer cells as the original, or primary, cancer. For example, breast cancer

that forms a metastatic tumor in the lung is metastatic breast cancer, not lung cancer.

Under a microscope, metastatic cancer cells generally look the same as cells of the original cancer. Moreover, metastatic cancer cells and cells of the original cancer usually have some molecular features in common, such as the presence of specific chromosome changes.

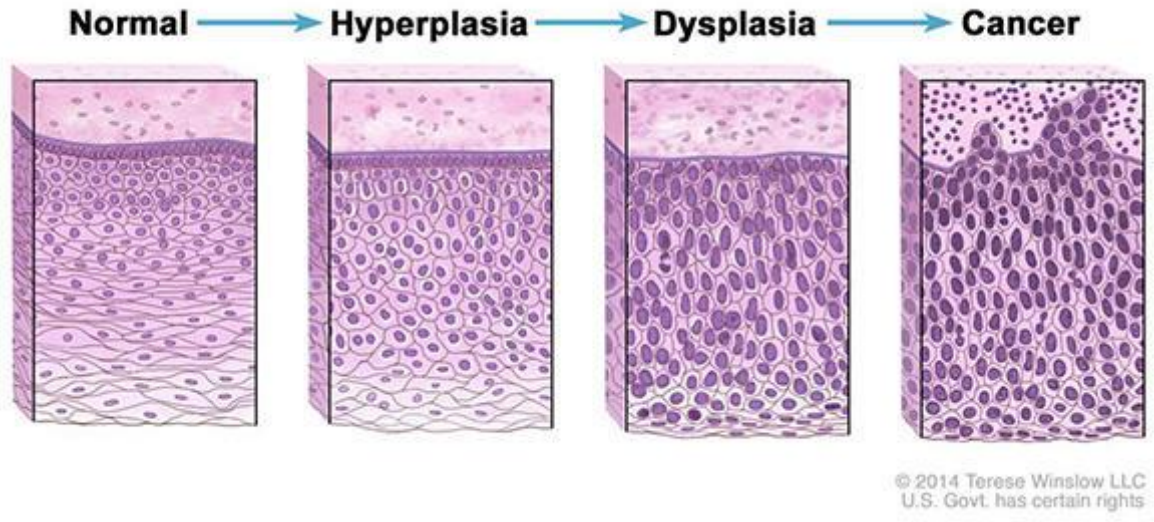
In some cases, treatment may help prolong the lives of people with metastatic cancer. In other cases, the primary goal of treatment for metastatic cancer is to control the growth of the cancer or to relieve symptoms it is causing. Metastatic tumors can cause severe damage to how the body functions, and most people who die of cancer die of metastatic disease.

Tissue Changes that Are Not Cancer

Not every change in the body's tissues is cancer. Some tissue changes may develop into cancer if they are not treated, however. Here are some examples of tissue changes that are not cancer but, in some cases, are monitored because they could become cancer:

- **Hyperplasia** occurs when cells within a tissue multiply faster than normal and extra cells build up. However, the cells and the way the tissue is organized still look normal under a microscope. Hyperplasia can be caused by several factors or conditions, including chronic irritation.

- **Dysplasia** is a more advanced condition than hyperplasia. In dysplasia, there is also a buildup of extra cells. But the cells look abnormal and there are changes in how the tissue is organized. In general, the more abnormal the cells and tissue look, the greater the chance that cancer will form. Some types of dysplasia may need to be monitored or treated, but others do not. An example of dysplasia is an abnormal mole (called a dysplastic nevus) that forms on the skin. A dysplastic nevus can turn into melanoma, although most do not.
- **Carcinoma in situ** is an even more advanced condition. Although it is sometimes called stage 0 cancer, it is not cancer because the abnormal cells do not invade nearby tissue the way that cancer cells do. But because some carcinomas in situ may become cancer, they are usually treated.



Normal cells may become cancer cells. Before cancer cells form in tissues of the body, the cells go through abnormal changes called hyperplasia and dysplasia. In hyperplasia, there is an increase in the

number of cells in an organ or tissue that appear normal under a microscope. In dysplasia, the cells look abnormal under a microscope but are not cancer. Hyperplasia and dysplasia may or may not become cancer.

Credit: © Terese Winslow

Types of Cancer

There are more than 100 types of cancer. Types of cancer are usually named for the organs or tissues where the cancers form. For example, lung cancer starts in the lung, and brain cancer starts in the brain. Cancers also may be described by the type of cell that formed them, such as an epithelial cell or a squamous cell.

You can search NCI's website for information on specific types of cancer based on the cancer's location in the body or by using our A to Z List of Cancers. We also have information on childhood cancers and cancers in adolescents and young adults.

Here are some categories of cancers that begin in specific types of cells:

Carcinoma

Carcinomas are the most common type of cancer. They are formed by epithelial cells, which are the cells that cover the inside and outside surfaces of the body. There are many types of epithelial cells, which often have a column-like shape when viewed under a microscope.

Carcinomas that begin in different epithelial cell types have specific names:

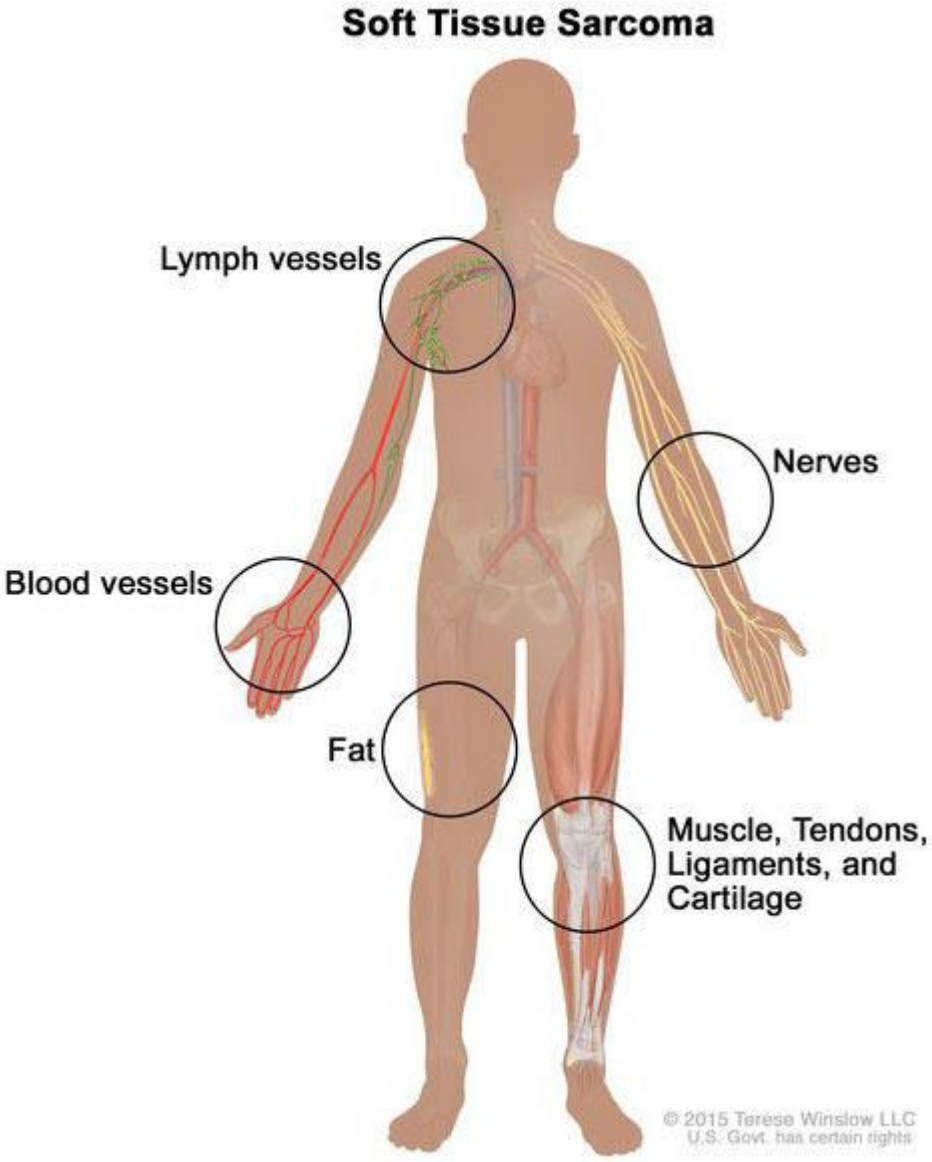
Adenocarcinoma is a cancer that forms in epithelial cells that produce fluids or mucus. Tissues with this type of epithelial cell are sometimes called glandular tissues. Most cancers of the breast, colon, and prostate are adenocarcinomas.

Basal cell carcinoma is a cancer that begins in the lower or basal (base) layer of the epidermis, which is a person's outer layer of skin.

Squamous cell carcinoma is a cancer that forms in squamous cells, which are epithelial cells that lie just beneath the outer surface of the skin. Squamous cells also line many other organs, including the stomach, intestines, lungs, bladder, and kidneys. Squamous cells look flat, like fish scales, when viewed under a microscope. Squamous cell carcinomas are sometimes called epidermoid carcinomas.

Transitional cell carcinoma is a cancer that forms in a type of epithelial tissue called transitional epithelium, or urothelium. This tissue, which is made up of many layers of epithelial cells that can get bigger and smaller, is found in the linings of the bladder, ureters, and part of the kidneys (renal pelvis), and a few other organs. Some cancers of the bladder, ureters, and kidneys are transitional cell carcinomas.

Sarcoma



Soft tissue sarcoma forms in soft tissues of the body, including muscle, tendons, fat, blood vessels, lymph vessels, nerves, and tissue around joints.

Credit: © Terese Winslow

Sarcomas are cancers that form in bone and soft tissues, including muscle, fat, blood vessels, lymph vessels, and fibrous tissue (such as tendons and ligaments).

Osteosarcoma is the most common cancer of bone. The most common types of soft tissue sarcoma are leiomyosarcoma, Kaposi sarcoma, malignant fibrous histiocytoma, liposarcoma, and dermatofibrosarcoma protuberans.

Our page on soft tissue sarcoma has more information.

Leukemia

Cancers that begin in the blood-forming tissue of the bone marrow are called leukemias. These cancers do not form solid tumors. Instead, large numbers of abnormal white blood cells (leukemia cells and leukemic blast cells) build up in the blood and bone marrow, crowding out normal blood cells. The low level of normal blood cells can make it harder for the body to get oxygen to its tissues, control bleeding, or fight infections.

There are four common types of leukemia, which are grouped based on how quickly the disease gets worse (acute or chronic) and on the type of blood cell the cancer starts in (lymphoblastic or myeloid). Acute forms of leukemia grow quickly and chronic forms grow more slowly.

Our page on leukemia has more information.

Lymphoma

Lymphoma is cancer that begins in lymphocytes (T cells or B cells). These are disease-fighting white blood cells that are part of the

immune system. In lymphoma, abnormal lymphocytes build up in lymph nodes and lymph vessels, as well as in other organs of the body.

There are two main types of lymphoma:

Hodgkin lymphoma – People with this disease have abnormal lymphocytes that are called Reed-Sternberg cells. These cells usually form from B cells.

Non-Hodgkin lymphoma – This is a large group of cancers that start in lymphocytes. The cancers can grow quickly or slowly and can form from B cells or T cells.

Our page on lymphoma has more information.

Multiple Myeloma

Multiple myeloma is cancer that begins in plasma cells, another type of immune cell. The abnormal plasma cells, called myeloma cells, build up in the bone marrow and form tumors in bones all through the body. Multiple myeloma is also called plasma cell myeloma and Kahler disease.

Our page on multiple myeloma and other plasma cell neoplasms has more information.

Melanoma

Melanoma is cancer that begins in cells that become melanocytes, which are specialized cells that make melanin (the pigment that gives skin its color). Most melanomas form on the skin, but melanomas can also form in other pigmented tissues, such as the eye.

Our pages on skin cancer and intraocular melanoma have more information.

Brain and Spinal Cord Tumors

There are different types of brain and spinal cord tumors. These tumors are named based on the type of cell in which they formed and where the tumor first formed in the central nervous system. For example, an astrocytic tumor begins in star-shaped brain cells called astrocytes, which help keep nerve cells healthy. Brain tumors can be benign (not cancer) or malignant (cancer).

Our pages on brain and spinal cord tumors in adults and brain and spinal cord tumors in children have more information.

Other Types of Tumors

Germ Cell Tumors

Germ cell tumors are a type of tumor that begins in the cells that give rise to sperm or eggs. These tumors can occur almost anywhere in the body and can be either benign or malignant.

Our page of cancers by body location/system includes a list of germ cell tumors with links to more information.

Neuroendocrine Tumors

Neuroendocrine tumors form from cells that release hormones into the blood in response to a signal from the nervous system. These tumors, which may make higher-than-normal amounts of hormones, can cause many different symptoms. Neuroendocrine tumors may be benign or malignant.

Our definition of neuroendocrine tumors has more information.

Carcinoid Tumors

Carcinoid tumors are a type of neuroendocrine tumor. They are slow-growing tumors that are usually found in the gastrointestinal system (most often in the rectum and small intestine). Carcinoid tumors may spread to the liver or other sites in the body, and they may secrete substances such as serotonin or prostaglandins, causing carcinoid syndrome.

Primary prevention of cancer

Key message:

1. One third to one half of cancer cases could be prevented by reducing exposure to known risk factors. Examples of actionable interventions are tobacco control and HPV vaccination.

2. Most countries do not fully implement cancer prevention policies and programmes, resulting in millions of avoidable cancer cases

3. The most effective approach to primary prevention of cancer involves the whole-of-government, with a combination of legislation, regulation and fscal policies and activities to change community and individual behaviour. Public health messages and promotion should include evidence for specifc risk factors.

Public health approaches to cancer primary prevention:

Primary prevention of cancer comprises a broad spectrum of interventions: legislation and policies to minimize or eliminate exposure to carcinogens; promotion of healthy behaviour; health sector programmes such as vaccination and clinical counselling for tobacco cessation. These strategies require a wholeof-government, whole-of-society approach Many risk factors for cancer are also risk factors for other NCDs, including tobacco use, harmful use of alcohol, physical inactivity, unhealthy diet and air pollution. Therefore, cancer

prevention programmes and policies should be integrated into a broader national or regional NCD strategy for greater effciency and impact. Other risk factors might be included in a coherent response for comprehensive cancer prevention. IARC working groups have identifed more than 100 carcinogens, many of which can be controlled through regulation or legislation. Infectious agents are responsible for 13% of cancers globally and predominantly affect lower socioeconomic and vulnerable populations (2). Such agents are therefore often amenable to public health responses that promote equity).

Programmes for hepatitis B vaccination at birth, particularly in endemic countries like China, have signifcantly reduced the incidence of primary liver cancer. Progress in reducing the burden of liver disease will be made through the global health sector strategy to eliminate viral hepatitis as a public health threat by 2030.

The Mission of the Division of Cancer Prevention (DCP)

“The NCI Division of Cancer Prevention leads, supports, and promotes rigorous, innovative research and training to reduce risks, burdens, and consequences of cancer to improve the health of all people.”

NCI’s Division of Cancer Prevention: Vision Philip E. Castle, PhD, MPH On behalf of the Division of Cancer Prevention, NCI/NIH/DHHS December 9, 2021 2 Cancer Burden 3 The Mission of the Division of Cancer Prevention (DCP) “The NCI Division of Cancer Prevention leads, supports, and promotes rigorous, innovative research and training to reduce risks, burdens, and consequences of cancer to improve the health of all people.” 4 Protocol Information Office Troy Budd Cancer Biomarkers Research Group Sudhir Srivastava, Ph.D., M.P.H. Nutritional Science Research Group Harold Seifried, Ph.D., D.A.B.T. Biometry Research Group Victor Kipnis, Ph.D. Early Detection Research Group Paul Pinsky, Ph.D. Gastrointestinal and Other Cancer Research Group Asad Umar, D.V.M., Ph.D. Breast and Gynecologic Cancer Research Group Brandy Heckman-Stoddard, Ph.D., M.P.H. Lung and Upper Aerodigestive Cancer Research Group Eva Szabo, M.D. Prostate and Urologic Cancer Research Group Howard Parnes, M.D. Office of the Director Phil Castle, Ph.D., M.P.H. Deputy Director Lori Minasian, M.D. Associate Director for Clinical Research Leslie Ford, M.D. Community Oncology and Prevention Research Group Worta McCaskill-Stevens, M.D., M.S. Chemopreventive Agent Development Research Group Robert Shoemaker, Ph.D. Cancer Prevention Fellowship Program Lisa Signorello, Ph.D. Organizational Structure Translational Research at the National Cancer Institute Division of Cancer Prevention (DCP) • Preventive Agents • Biomarkers for Screening and Early Detection •

Symptom Science, Prevention, & Management T0 T1 T2 T3 T4 6 Extramural/Stakeholder Engagement (Examples) ▪ Multi-Cancer Early Detection Study Design Workshop (Dr. Lori Minasian & the MCED "Tiger Team") ▪ Cancer Screening Workshop (Drs. Paul Pinsky and Brandy Heckman-Stoddard) ▪ Translational Advances in Cancer Prevention Agent Development Virtual Workshop on Immunomodulatory Agents (Drs. Mark Miller & Altaf Mohammed) ▪ Cannabis Workshop (Dr. Alexis Bakos, DCCPS, DCTD, FDA, NIDA) ▪ FNIH Cancer Prevention Workshop (Drs. Lori Minasian & Leslie Ford) ▪ FDA-NCI Mini-Symposium on Cancer Prevention and Risk Reduction (Dr. Brandy Heckman-Stoddard) ▪ Initiated new FDA-NCI working group on cancer prevention (CDER, CBER, and CDRH) ▪ IPAs with KOLs/Experts (in progress) ▪ New engagements with industry partners!!! 7 Cancer Prevention: Avoidance, Vaccination (1o Prevention), & Screening & Treatment/Interception (2o Prevention) (Adapted from Nat Rev Cancer 2012, 12:835) Precursor States Carcinogen Avoidance/Early Treatment: ➢ Tobacco Prevention ➢ Human papillomavirus Vaccination ➢ Hepatitis B Vaccination ➢ Treatment of H. pylori Tobacco Cessation Screening, Diagnosis, & Removal (excision)/ Destruction (ablation) for Cancer Risk Reduction: polyps & intraepithelial neoplasia (IN), and prophylactic surgeries 8 Interception of Cancer Molecular prevention and immunoprevention with targeted agents and immune modulators (Adapted from Nat Rev Cancer 2012, 12:835) Precursor States Agents targeting specific pathways: ▪ Tamoxifen and its derivatives for breast cancer ▪ NSAIDS

for colon cancer ▪ Immune modulators such as STAT-3 inhibitors ▪ Drugs targeting oncogenic drivers (e.g., mTOR inhibitor, EGFR inhibitors, and PARP Inhibitors) ▪ Reactivators of tumor suppressor genes (ONC-201) 9 Preventive Agent R&D Pipeline Basic Science Research Translation to Humans Translation to Patients Translation to Practice Translation to Community CAP-IT PREVENT CP-CTNet NCORP Investigator-Initiated Research Moonshot: Novel Adjuvants ULACNet Cancer Prevention & Control Clinical Trials (PAR-21-035) "Clinical Trials Planning & Feasibility" 10 DCP Cancer Preventive Agent Pipeline (Drs. Sei and Shoemaker I) Proof of Concept (Evaluate Activity) II) Secondary Testing (Confirm Efficacy) III) Advanced Preclinical Development (CGMP, GLP, & IND) Approved Concepts Clinical Development Team CAP-IT Go/No-Go Go/No-Go Go/No-Go Clinical Trials Networks CP-CTNet PREVENT Cancer Program 11 Cancer Prevention Clinical Trials Network (CP-CTNet) (Eva Szabo, MD) ▪ Design/conduct early phase clinical trials to assess the safety, tolerability, and cancer preventive potential ▪ Additional goals: ➢ Optimize clinical trial designs ➢ Develop surrogate and intermediate endpoint biomarkers ➢ Test novel imaging technologies ➢ Develop further insights into mechanisms of cancer prevention by agents MD Anderson CC U Arizona Northwestern U Wisconsin U. Michigan 12 Examples of Recent Protocols in the CP-CTNet ▪ Lisinopril to Prevent Progression of Non-Alcoholic Fatty Liver Disease (▪ Nonavalent Prophylactic HPV Vaccine to Assess Immunogenicity of A Prime and Deferred-Booster Dosing Schedule among 9-11 Year-old Girls and

Boys (Delayed Booster Trial- An Extended Follow-up Study) ▪ Clinical Study of Bioactivity of Low-Dose Apalutamide in Prostate Cancer Patients Scheduled for Prostatectomy ▪ Surgical Window of Opportunity Study of Megestrol Acetate Compared with Megestrol Acetate and Metformin for Endometrial Intraepithelial Neoplasia ▪ Targeting Dominant-Negative Missense Mutant p53 by Atorvastatin for Reducing the Risk of Longstanding Ulcerative Colitis-Associated Cancer: Two-Arm, Randomized and Placebo-Controlled Phase II Trial 13 Screening and Early Detection (Adapted from Nat Rev Cancer 2012, 12:835) Screening for the prevention and control of breast, cervical, colorectal, lung, HCV (for liver), and prostate cancer in asymptomatic adults; targeted screening of higher-risk individuals for the prevention of less common but still important cancers Precursor States Risk-informed screening: higher risk = more screening and/or different management, and potential for intervention with targeted preventive agents 14 Screening and Early Detection R&D Pipeline Basic Science Research Translation to Humans Translation to Patients Translation to Practice Translation to Community Investigator-Initiated Research TBEL HTAN PCA Alliance of GBs SCLC EDRN NCORP PCDC TLC LBC CIB Last Mile PLCO NLST LDCT Interpretation ULACNet Cascade Cancer Prevention & Control Clinical Trials (PAR-21-035) “Clinical Trials Planning & Feasibility” 15 Clinical Validation Centers (CVC) Validation Biomarker Developmental Laboratories (BDL) Discovery Biomarker Reference Laboratories (BRL) Assay Development Network Consulting Team Steering & Executive

Committees Data Management & Coordinating Center (DMCC) EDRN Collaborations & Partners ▪ Parallel, EDRN-Advised Initiatives: ▪ Co-funding e.g., PanCAN, Canary Foundation, & Cancer Research UK ▪ Independent, collaborative groups e.g., Pancreatic Cancer Detection Consortium, Consortium for Imaging and Biomarkers, Human Tumor Atlas Network (PreCancer Atlas), & Center for Global Health (NCI) ▪ Associate Members (>350) ▪ Federal Partners e.g., NIST, FDA, & Jet Propulsion Lab (JPL) ▪ Pharma/Biotech Industry (15 active) Research Groups ➢ Prostate & Other Urologic ➢ Breast and Other Gynecologic ➢ Lung & Upper Aerodigestive ➢ Colon & Other GI EDRN Organizational & Operational Structure (Dr. Sudhir Srivastava) 16 NCI Community Oncology Research Program (NCORP) (Worta McCaskill-Stevens, MD, MS) 1,000+ Clinical Sites (46 Centers & Affiliates), 4,000+ Investigators 17 ▪ Primary endpoint remains as occurrence of advanced cancer. However, assessment approach was modified: ➢ Original design: occurrence of advanced cancer within a fixed time period of 4.5 years from randomization (binary endpoint, binomial comparison). Screening schedule of participants does not change. ➢ Revised design: occurrence of advanced cancer at any time up to 7 years from randomization (time-to-event endpoint, comparison via logrank test). ▪ Power lowered to 85% from original 90% (Reduced sample size of 36K). Derivation of sample size continues to assume 20% relative reduction in advanced cancer at 4.5 years from randomization. ▪ Study duration: 10 years (7-

year accrual, 3-year follow-up). Projected completion date: Aug 30, 2027 TMIST (NCORP) Design Modifications 18 TMIST (NCORP) Accrual (12/1/2021): 60,422 New accrual target: 129,000 Minority Accrual=28% ▪ 20% Black/African American Women ▪ 6% Hispanic Women ▪ 2% Women of Other Racial/Ethnic Groups 19 Large Screening/ Management Trials • FORTE: Five- or ten-year colonoscopy for 1-2 nonadvanced adenomatous polyps • TMIST: Randomized to 2D digital mammography versus 3D tomosynthesis mammography for 4 years; primary endpoint is reduction in advanced cancers Other Studies • Comparing the clinical impact on pancreatic cyst low versus high intensity surveillance • Comparing the noninferiority of salpingectomy to salpingo-oophorectomy to reduce the risk of ovarian cancer among BRCA1 carriers Symptom Management & Quality-of-Life Trials • Immune Checkpoint Inhibitor Toxicity (I-CHECKIT): A Prospective Observational Study • Optimizing Functional Outcomes of Older Cancer Survivors After Chemotherapy Examples of Research Under Way or Recently Approved by the NCORP Steering Committee 20 Screening and Early Detection R&D Pipeline Basic Science Research Translation to Humans Translation to Patients Translation to Practice Translation to Community Investigator-Initiated Research Trans-NCI Liquid Biopsy/MultiCancer Early Detection Program 21 MCED Study Design Workshop (Dr. Lori Minasian) ▪ Current knowledge on MCED assays focuses on diagnostic performance ➢ Sensitivity is modest for early stage, greater for advanced stage ➢ Specificity appears to be high (97%

or higher) ▪ Clinical utility of widespread implementation of MCED testing is unknown ➢ Favorable diagnostic performance does not always translate to satisfactory outcome ➢ Risks and harms associated with using MCED for cancer screening are not known ▪ MCED tests present novel implementation challenges ➢ How to quickly and reliably confirm cancer status and site after a positive test ➢ How best to screen for multiple cancers with different latency periods 22 Themes that Emerged from the Workshop ▪ NCI needs to support a trial to evaluate MCED assays ➢ Rigorously assess risk and benefits from the screening process ➢ Comparison for a trial would be MCED assay + standard of care screening versus standard of care screening alone ▪ Several unknowns for the screening process ➢ Variability in diagnostic workup o Different assays may or may not point to a "tissue of origin " for the workup o Even with a tissue "locator," the follow up testing to reach a diagnostic resolution varies with providers and patients' access to further diagnostic studies and willingness to complete those diagnostic studies (time away from work, etc.) ➢ Need to assess the full process for the workup and when to stop the workup 23 Additional Themes Discussed ▪ Assure enrollment of various populations ➢ Underserved populations ➢ Diverse populations ➢ Vulnerable (socio-economically disadvantaged, others) ➢ High-risk individuals ▪ Need concrete process for the recruitment: ➢ Communication strategy to include a combination of remote and in-person recruitment approaches

▪ Need to assure means for adequate follow up to occur and not inadvertently or disproportionally expose vulnerable people to the harms 24 My Holy Grail: Precision Cancer Prevention Biomarker Pipeline Preventive Agent Pipeline Discovery Early Validation Efficacy DETECT & MITIGATE Discovery Early Validation Efficacy CANCER RISK 25 Symptom Science and Management (Adapted from Nat Rev Cancer 2012, 12:835) Precursor States Basic research to uncover mechanisms and markers of risk for adverse events 3 o prevention with chemotherapy, immunotherapy, surgery, radiation therapy, and hormonal therapy Prevention and management of symptoms of cancer and cancer treatment 26 Symptom Mgt/Supportive Care R&D Pipeline Basic Science Research Translation to Humans Translation to Patients Translation to Practice Translation to Community Investigator-Initiated Research NCORP Moonshot: Tolerability Consortium • RFAs CA-15-008, 16-010, 18- 019 (Provocative Questions) • PAR-19-325 • RFA-17-052 27 Symptom Management and Toxicity Mitigation ▪ Understand mechanisms of action for the chronic adverse effects ➢ Investigator community interested in exploring mechanisms of adverse effects of cancer treatment to normal tissue ➢ Provocative question RFA had significant response ▪ Rigorously characterize the clinical syndrome for the toxicity or symptom ➢ Need appropriate and robust measures for symptomatic toxicities o Examples: chemotherapy induced peripheral neuropathy and cancer-related fatigue ➢ Need longitudinal studies to

evaluate the natural history of the toxicity ➢ Current approach is to capture most severe event using CTCAE at single point in time ▪ Capture how the patient functions & feels through patient reported outcomes ➢ Symptom management and toxicity mitigation trials frequently have PROs as the primary endpoint ➢ Need systematic approach to collection, analysis and reporting of PRO data 28 Trans-NCI Research Opportunities ▪ Provocative Question: ➢ PQ9 or 12: What are the molecular and/or cellular mechanisms that underlie the development of cancer therapy-induced severe adverse sequelae? ➢ RFAs CA-15-008, 16-010, 18-019 ▪ Clinical Characterization of Cancer Therapy-Induced Adverse Sequelae and Mechanism-Based Interventional Strategies ➢ PAR-19-325 ➢ Specifically, identified the need for longitudinal phenotyping projects ▪ Analyzing and Interpreting Clinician and Patient Adverse Event Data to Better Understand Tolerability ➢ RFA-17-052 29 Cannabis, Cannabinoids, and Cancer (Dr. Alexis Bakos) ▪ Virtual Workshop December 2020 ▪ Members from multiple NCI divisions, FDA, and NIDA ▪ Monograph published last week (Volume 2021 Issue 58 | JNCI Monographs | Oxford Academic (oup.com)) 30 Final Comments: Some Proposed DCP Priorities ▪ Biological & Population Risk-Informed Interventions: ➢ Biological Risk --- Targeted interventions (agents or biomarkers) based on the biology/pathways of carcinogenesis, i.e., “precision cancer prevention” ➢ Population Risk --- Using risk to decide who gets screened and how, how screen+ are managed, and harmonizing care

i.e., “equal care for equal risk” ▪ Obesity: ≥20% of cancers are attributable to obesity but we do not really understand how obesity contributes to carcinogenesis. If we did, we could mitigate its effects. ▪ Symptom Science/Precision Symptom Prevention & Management: How can we use biology, genetics, and epidemiology to: ➢ Understand the “etiology” of symptoms (symptom science) ➢ Explain adverse responses to treatments ➢ Move symptom management from trial-and-error to precision medicine 31 Final Comments: Some Proposed DCP Priorities ▪ Health Disparities: Innovations in technologies (e.g., self-collection, POC testing, etc.) to bring standard-of-care (or better) to underserved populations who are typically at higher risk of cancer. ▪ New Technologies: AI, multi-cancer early detection, synthetic biomarkers, etc., etc. We need to get out front and figure out what is good and what is not. ▪ Immunology and Preventive Vaccination: What constitutes an effective immune response to a carcinogenic insult; neoantigen discovery and validation 32 Final Comments: Redefining Precision Cancer Prevention to Promote Health Equity* ▪ Maximizing Benefits to Harms for the Entire Population (B:H) ▪ Understanding all causes of differences---not just biological---informs how we can be more “precise” Who: use population risk to decide needs the intervention What: use biological risk for a targeted approach Where: increasing access by alternative healthcare delivery strategies How: B:H can be increased by alternative routes of administration to increase bioavailability at the target site and limit exposure at non-target sites

Current landscape of cancer prevention:

Adoption of effective cancer prevention policies and programmes has been inadequate, particularly in LMIC. Tobacco control remains the main prevention policy in nearly every country. Globally, 2.4 million deaths from cancer due to use of tobacco products occur every year (8). Tobacco use is a risk factor for at least 20 cancer types and for other medical conditions, such as cerebrovascular disease, heart disease and chronic respiratory disease.

About 1.1 billion people in the world use tobacco products and consumption is often highest among people with the least education and income (Only two countries, however,Prevalence of tobacco smoking among people aged 15 years and older, 2018 3.2 Current landscape of cancer prevention have thus far fully implemented MPOWER measures. “MPOWER” is a set of measures to reduce the demand for tobacco products that is recommended by WHO and in line with the WHO FCTC to reduce the demand for tobacco products, as recommended by WHO and in line with the WHO FCTC

While there has been some progress, without accelerated action, tobacco will be responsible for over one billion deaths this century . During the past decade, there has been increasing uptake of electronic nicotine delivery systems (ENDS), including by children and adolescents. The effect on cancer incidence is not yet established, but these systems pose a new and signifcant public health risk.