

# Genetic and Molecular Basis of Cancer

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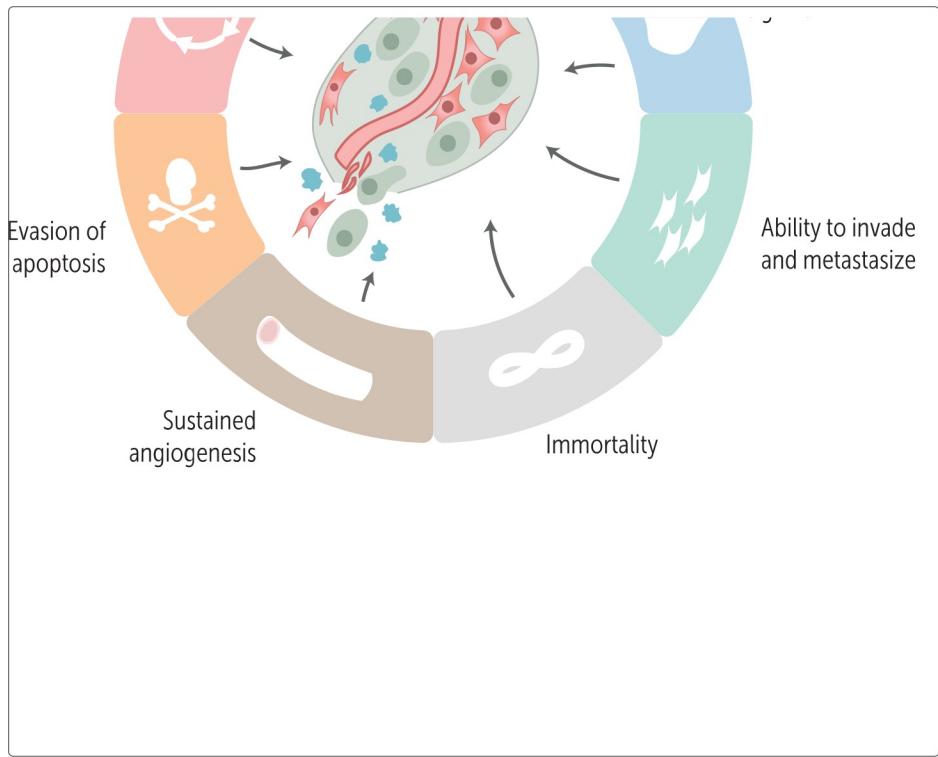
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## [Learning Objectives \(5\)](#)

*After completing this brick, you will be able to:*

- 1 Explain how nonlethal genetic damage is at the center of cancer pathogenesis.
- 2 List and describe the eight hallmarks of cancer cells.
- 3 Explain how cancer cell hallmarks are used in the diagnosis and treatment of cancer.
- 4 Describe the four classes of regulatory genes that are the main targets of cancer-causing mutations.
- 5 Describe the process of clonal expansion, and explain the concept of tumor subclones.



### QUIZ

Tap image for quiz

Figure 1

## Cancer Cells Grow Like Crazy

Several of these hallmarks have to do with the ability of cancer cells to grow like crazy. Normal cells need growth signals in order to grow, and

when they receive signals to stop growing, they stop. In contrast, cancer cells grow and divide without outside help—and they learn how to find and use energy sources to support an ever-increasing population of tumor cells.

- Cancer cells can grow on their own without any outside signals; this is called **autonomous cell proliferation**.
- Cancer cells can basically just ignore any signals telling them to stop growing, which we call **resistance to growth-suppressing signals**.
- Cancer cells have an **altered metabolism**, too: they use **anaerobic glycolysis** so that they can synthesize everything they need for rapid cell growth.

### INSTRUCTOR NOTE

Please note - Robbins and Cotran, the traditional textbook of Pathology in its most updated edition (11th, 2025) states that cancer cells use aerobic NOT anaerobic glycolysis - please see below and power point:

"Cancer cells demonstrate a distinctive form of cellular metabolism characterized by high levels of glucose uptake and increased conversion of glucose to lactate (fermentation) via the glycolytic pathway. This phenomenon, called the Warburg effect... also known as aerobic glycolysis.."

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- Cancer cells know how to stimulate the growth of new blood vessels (**angiogenesis**) so that as the tumor gets bigger, the blood supply is

able to keep up.

## Cancer Cells Refuse to Die

Cancer cells also don't die like normal cells do.

- Normal cells can only undergo a certain number of mitoses (usually around 60-70) before they die. But cancer cells are "**immortal**" and can replicate endlessly.
- Normal cells also have a preprogrammed script for a special kind of cell death called apoptosis—and they'll follow that script if they are told to do so. Cancer cells don't follow that script; they are able to **evade apoptosis**.
- Speaking of evasion, cancer cells are also able to **evade the host's immune response**, which typically kills any cell that displays abnormal antigens.

## Cancer Cells Metastasize

One final hallmark of cancer is **metastasis**, which refers to the ability of cancer cells to spread throughout the body. This hallmark more than any other is diagnostic of cancer. Some of these other characteristics are present even in benign tumor cells—but with very few exceptions, benign tumors do not metastasize.

## Cancer Cells Create the Right Conditions for Growth

Acquiring these eight hallmarks is not a simple or quick process. But cancer cells make this task easier by creating two cancer-enabling conditions:

- Genomic instability

- Genomic instability
- Cancer-enabling inflammation

Let's look at genomic instability first. As cancer cells evolve, they acquire gene mutations that enable them to bypass normal processes—such as DNA repair systems—that keep DNA intact and stable. As a result, the DNA of the cancer cell becomes even more susceptible to genetic mutations. This DNA condition is called genomic instability, and it paves the way for the cancer cell to acquire the hallmarks of cancer discussed above.

Another cancer-enabling condition is inflammation. As cancers invade tissues, they attract inflammatory cells such as lymphocytes and macrophages to the region of the tumor. Normally, inflammatory cells are very useful in the fight against foreign invaders. But in this scenario, the tumor manipulates the inflammatory cells into secreting factors that promote cancer cell growth, enhance the cancer cells' ability to resist death, and otherwise enable the cancer cell on its hallmark-acquiring path.

## How Are Hallmarks Used in the Diagnosis and Treatment of Cancer?

We'll now go into more detail on four of those hallmarks of cancer that allow cancer to survive despite all of the checks and balances to prevent it:

- Altered metabolism
- Evasion of apoptosis
- Sustained angiogenesis
- Immortality

These four hallmarks merit a more in-depth discussion because they frequently are used as targets in the diagnosis and treatment of cancer. For example, the altered metabolism of cancer cells is the basis for positron

emission tomography (PET), a diagnostic imaging method that identifies cancer cells by detecting their abnormally high uptake and metabolism of glucose. Another example is traditional chemotherapy, which exploits the replicative immortality of cancer cells by specifically targeting rapidly dividing cells.

## Altered Metabolism

Each cell has metabolic processes that form (anabolic) or break down (catabolic) different molecules. These actions use substrates from the environment to provide energy for the cell. One of the most common sources of energy is glucose.

INSTRUCTOR NOTE

In the presence of oxygen usually glycolysis converts glucose to pyruvate which then enters the TCA cycle and oxidative phosphorylation. Whereas in the absence of oxygen, pyruvate is converted to lactic acid. But in the Warburg effect, the tumor cells can actually do glycolysis and then get pyruvate converted to lactic acid even if they have enough oxygen present. That's why it's called aerobic glycolysis - because the lactic acid fermentation occurs even in the presence of oxygen.

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Glucose can be processed for energy aerobically in the citric acid cycle and the electron transport chain. Or it can be processed anaerobically which

results in the production of lactate. Most cells with mitochondria use aerobic metabolism to generate energy in the presence of oxygen, whereas cells without mitochondria, like red blood cells, use the anaerobic process. Cells with mitochondria also resort to anaerobic glycolysis and produce lactate in the absence of oxygen. Cancer cells behave differently!

INSTRUCTOR NOTE

As per the Robbins text, "Why is it advantageous for a cancer cell to rely on seemingly inefficient glycolysis (2 molecules of ATP per molecule of glucose) instead of oxidative phosphorylation (36 molecules of ATP per molecule of glucose)? The answer: aerobic glycolysis provides rapidly dividing tumor cells with metabolic intermediates that are needed for the synthesis of cellular components, whereas mitochondrial oxidative phosphorylation does not."

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Although they have mitochondria, cancer cells preferentially metabolize glucose to lactate, even in the presence of abundant oxygen. We think this allows them to rapidly generate biosynthetic raw materials and energy for proliferation. This unique type of aerobic glycolysis in cancer cells is called the Warburg effect.

The altered metabolism of cancer cells is used to aid in the diagnosis of cancer and detection of metastasis via positron emission tomography (PET) scan. In this scan a radioactive tracer such as 18F-

PET scan. In this scan, a radioactive tracer, such as 18F-

fluorodeoxyglucose (18F-FDG), an analog of glucose, is administered. This is taken up by cells as if it is glucose. Since cancer cells have higher glucose uptake than noncancerous cells, the tracer is significantly absorbed by cancer cells, leading to bright areas visible on the PET scan.

## Evasion of Apoptosis

Apoptosis is programmed cell death, or cell suicide, and it is a normal cellular process. It often occurs when the cell is damaged. For example, when a cell has DNA damage that cannot be fixed, the cell will often induce apoptosis so as not to continue proliferating with this damage, because that could lead to cancer. Think of cancer cells as super cells that have bypassed this well-regulated process.

There are two different pathways to apoptosis: the extrinsic or death receptor-mediated pathway and the intrinsic mitochondrial pathway. Both pathways result in the production of caspases, protease enzymes that breakdown the nuclear and cytoplasmic components of the cell. Cancer cells can downregulate the expression of these caspases or modify their action through phosphorylation. In addition, the molecules in a normal cell that inhibit apoptosis such as the *Bcl-2* family of proteins and the inhibitor of apoptosis proteins (IAPs) are upregulated. This property can be used as a target for antitumor drugs, such as the *Bcl-2* inhibitor venetoclax, a treatment for hematologic malignancies.

How does a cancer cell avoid both the extrinsic and intrinsic pathways of apoptosis?

## Sustained Angiogenesis

As cancer cells proliferate rapidly, avoiding apoptosis and shifting their metabolism to anaerobic pathways, they need to find a way to increase their access to energy, specifically glucose. To accomplish this task, they increase the number of avenues that can provide the nutrients they need. This process is called angiogenesis, or the creation of new blood vessels.

In normal physiology, angiogenesis is regulated. In cancers, this regulation is disrupted. One of the most common angiogenesis signals upregulated by cancer cells is *vascular endothelial growth factor* (VEGF). VEGF is a ligand to *VEGF receptor tyrosine kinase*. This signaling pathway initiates the production of new blood vessels, which will bring glucose and oxygen to growing cancer cells. In addition, these blood vessels create new avenues through which cancer cells can enter and travel to new parts of the body, a process known as metastasis. Several antitumor drugs take advantage of this upregulation of VEGF; *monoclonal antibodies* against VEGF are used in the treatment of many solid tumors, such as colorectal cancer.

## Immortality

Most cells in the body have an internal limit to the number of times they

MOST cells in the body have an internal limit to the number of times they can replicate. This limit is determined by the length of telomeres, pieces of DNA that are like caps on the end of chromosomes. Each time a cell divides, the telomere shortens. Once the telomere disappears—usually after around 60-70 doublings—the cell can no longer replicate. Cancer cells have mutated to resist this end to their growth.

Cancer cells learn how to generate telomerase, an enzyme that replenishes telomeres after each mitotic division, restoring them to their original length. This action essentially makes the cell able to divide forever. Cancer treatments may be developed to either decrease the function of telomerasess or induce telomere dysfunction to combat this ability.

What does telomerase do to telomeres in cancer cells?

## Which Genes Are the Main Targets of Cancer-Causing Mutations?

Some genes are targeted more often than others by cancer-causing mutations. Can you guess why? If you thought that it might be the genes that induce the actions we described in the previous section, you would be 100% correct! Here, we will look at four classes of genes targeted by cancer-causing mutations and specific examples of each.

### Growth-Promoting Oncogenes

The first class is growth-promoting oncogenes. In normal cells, these genes are referred to as proto-oncogenes and they encode proteins that promote cell growth. However, a single gain-of-function mutation in such a gene can drive a cell toward cancer. This event changes the proto-oncogene to an oncogene, an overactive or overexpressed form of the proto-oncogene. In other words, a gene that originally had one function has gained a new function or increased the action of one of its previous functions. This change results in the cell's propensity toward cancer.

The National Cancer Institute developed a car analogy that we love for understanding how this works. Normally when driving your car, you ease off the gas pedal when you spot something that should slow you down. Imagine hitting a patch of traffic and not slowing down your car at all, instead keeping your foot planted on the gas pedal. A gain-of-function mutation is like having that accelerator pedal stuck on, full speed ahead, regardless of the danger ahead (Figure 2).

## QUIZ

 Tap image for quiz

**Figure 2**

Some examples of proto-oncogenes include Src, RTK, CTK, Myc, and Ras. Src is a nonreceptor tyrosine kinase; RTK is a receptor tyrosine kinase (eg, EGFR,  $\gamma$ EGF—growth factor receptors); and CTK is a cytoplasmic tyrosine kinase (eg, BCR-ABL—the Philadelphia chromosome). In normal cells, these receptors function to initiate signaling cascades through phosphorylation, which promote cell survival and growth. In cancer cells, these receptors are overexpressed or constitutively active, allowing the cell to survive and grow even in the presence of a mutation or a poor environment. Myc is a transcription factor that can be induced at the end of tyrosine kinase or non-tyrosine kinase pathways. As it is an integral stimulator of cell growth and survival, cells have many pathways to upregulate its expression. When it is mutated, the cell continues to grow and survive even with mutations or in a difficult environment.

Ras is unique in comparison with these receptors in that it is a G-coupled protein that resides in the cell membrane. The G stands for GTP. When GTP is not phosphorylated or in the GDP state, the Ras protein is inactive and cannot begin the signaling pathway. When GDP is phosphorylated to GTP, Ras activates its pathway. Aside from cell survival and cell growth,

Ras also initiates transcription, cell cycle progression, cell migration, and endocytosis. When these pathways are overstimulated, these actions can cause cells to become cancerous as they would have the ability to grow, survive, multiply, take in other items from the environment, and move.

## Growth-Inhibiting Tumor Suppressor Genes

Whereas oncogenes result from a gain-of-function mutation, tumor suppressor genes lead to cancer by a loss-of-function mutation. In other words, a gene that is usually expressed in the cell is now no longer being expressed, and the molecule it created is no longer working. Furthermore, unlike proto-oncogenes, which require only a single mutation, tumor suppressor genes require two mutation events to effectively become inactive. This route of mutation is known as the “two-hit hypothesis.” Basically, one allele can have a mutation from an initial event, and you will see no effect in the function of the cell. Then, another mutation event occurs in the other allele, resulting in a total lack of tumor suppressor gene function.

In the case of the car you were driving earlier, imagine if your car had two brakes. One of those brakes stopped working, but you still had the spare. Then, the other broke too. Now, you are moving forward toward your destination because you no longer have brakes to stop you (Figure 3).

**Figure 3**

Two examples of tumor suppressor genes include retinoblastoma (RB) and p53. *RB* and *p53* encode proteins that impede the progression of the cell cycle from the G1 phase (ie, all cellular contents duplicate except the chromosomes) to the S phase (ie, synthesis phase or chromosome duplication phase). The Rb protein (product of the *RB* gene) acts as a growth suppressor, and its inactivation results in inappropriate cell proliferation. *p53* is activated when there are hyperproliferative signals, DNA damage, telomere shortening, or hypoxia and causes cell cycle arrest, senescence, or apoptosis. When inactivated, the cell continues to proliferate even with these issues.

INSTRUCTOR NOTE

There is a significant clinical correlation associated with the tumor suppressor gene *p53*. There are families in which some members inherit one mutated allele. Therefore, based on the "two-hit" hypothesis above, they only need one more hit for cancer to develop. These families usually have members who develop

carcinomas, sarcomas, leukemias, lymphomas, etc., before the age of 50 years. This is known as Li Fraumeni syndrome and is important to keep in mind.

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Oncogenes step on the gas (gain-of-function). Tumor suppressor genes remove the brakes (loss-of-function).

### Genes That Regulate Programmed Cell Death (Apoptosis)

Remember discussing the avoidance of apoptosis by cancer cells? It turns out that there are two anti-apoptotic protein classes: certain members of the Bcl-2 family and the inhibitor of apoptosis proteins (IAPs) are critical for cancer cells to avoid apoptosis.

The Bcl-2 family of proteins has three groups, two pro-apoptotic and one anti-apoptotic. The anti-apoptotic group includes Bcl-2, Bcl-x<sub>L</sub>, and Mcl-1.

Bcl-2 and Bcl-x<sub>L</sub> prevent the release of a cytochrome c, a molecule from mitochondria that triggers the apoptotic process. Mcl-1 protects the cell against hypoxic conditions and other events that induce oxidative stress on the cell. On the other hand, IAPs block caspases. If you recall, caspases are part of the apoptotic pathway. When either the anti-apoptotic Bcl-2 family of proteins or IAPs are overexpressed, a cell can bypass apoptosis even if the conditions would usually promote cell suicide.

How does overexpression of Bcl-2 lead to cancer?

## Genes Involved in DNA Repair

Without successful DNA repair, cells begin to proliferate with mutations. More mutations mean higher chances of developing cancer. The cell has several ways to fix these mutations: DNA mismatch repair, nucleotide excision repair, base excision repair, and double-strand break repair. Double-strand break repair can be completed by homologous recombination repair or nonhomologous end joining.

### Homologous recombination repair or nonhomologous end joining.

Let's take a look at homologous recombination repair more in depth.

In this process, a double-strand break occurs in the DNA due to x-rays, free radicals, or another injury-causing event. After the initial detection of a DNA break, the second step involves several proteins, which form a nucleoprotein filament (ie, a compound that has DNA and protein). The first strand receiving this addition will be known as the leading strand. Then, other proteins help find a homologous portion of the parent DNA to form a template for the lagging strand. The lagging strand elongates with the help of DNA polymerase. Then, the leading strand unites with the lagging strand through DNA polymerase and ligase, resulting in the repair of the double-strand break.

The second step that formed the nucleoprotein filament involves two very well-known proteins: BRCA1 and BRCA2. When these proteins are mutated, homologous recombination repair or nonhomologous end joining (ie, another double-strand break repair mechanism that does not require homologous DNA strands) cannot happen or does not happen as efficiently. This event results in the incomplete repair of DNA and the progression of mutations within the cell, which can result in cancer ([Table 1](#)).

**Table 1 Double-strand DNA repair mechanisms and clinical implications**

	<b>Homologous recombination repair (HRR)</b>	<b>Nonhomologous end joining (NHEJ)</b>
Type of damage repaired	Double-strand breaks	Double-strand breaks
Cause of damage	Gamma rays, x-rays, replication errors, free radicals,	Gamma rays, x-rays, replication errors, free radicals,

	antineoplastic drugs, DS exonucleases	antineoplastic drugs, DS exonucleases
Key proteins/mechanism	BRCA1 and BRCA2, RAD51	BRCA1 and BRCA2, RAD51
Disease connections	Familial breast cancers and ovarian cancer	Severe combined immunodeficiency

## Why Is Cancer So Difficult to Destroy?

Now that we have reviewed the events that can happen to turn a cell cancerous, let's take a look at how cancer becomes more than just one mutated cell. Typically, the mutation that a cancer cell acquires increases the cell's fitness. When a cell's fitness is improved, it has the ability to produce more daughter cells (ie, divide more rapidly) than a normal cell without the mutation. This process of one cell giving rise to many identical daughter cells is called **clonal expansion**.

Sometimes, cancer daughter cell clones develop additional mutations. These additional mutations make these cells even stronger and fitter than the original cancer cells. These cells are known as **subclones**. Subclones are one reason why treating cancer can be so difficult. One treatment may work on the original cancer cell and its clones. However, new subclone tumor cells may arise that are impervious to the original treatment, allowing these cells to continue to grow and metastasize despite treatment. This occurrence is one of the greatest challenges in treating cancer.

quickly?

You explain that cancer cells can shift their metabolism to generate more energy needed to grow, bypass normal conditions that lead to cell death, produce new blood vessels to bring them fuel, and develop the ability to divide forever. All of these factors make cancer cells invincible. "It sounds incredible, and sometimes like a science fiction movie, but it's true. But we can target your treatment to what we know is effective," you say.

## Summary

- Nonlethal genetic damage is at the center of cancer pathogenesis.
- There are eight hallmarks of cancer cells that distinguish them from normal cells: those resulting in increased cell growth (autonomous cell proliferation, resistance to growth-suppressing signals, altered metabolism, angiogenesis), those resulting in decreased cell death (immortality, evasion of apoptosis, evasion of host immune response), and the ability to metastasize.
- Cancer cells acquire these eight hallmarks through the creation of genomic instability and cancer-enabling inflammation.
- Changes in metabolism (the Warburg effect), avoidance of apoptosis, stimulation of angiogenesis, and limitless replication are four critical hallmarks of cancer cells that can be targeted for cancer diagnosis and treatment.
- Growth-promoting proto-oncogenes, growth-inhibiting tumor suppressor genes, genes that regulate programmed cell death (apoptosis), and genes involved in DNA repair are all targets for cancer-related mutation and allow for cancer cells to continuously

grow and proliferate.

- Clonal expansion is the process by which a single cancer cell produces huge numbers of identical cancer cells.
- Tumor subclones with new mutations may emerge over time, and these new subclones may be resistant to the original treatment method; tumor subclones are one of the reasons why cancer is so difficult to treat.

B. *BRCA2*

C. p53

D. Ras

E. *RB*

## Review Questions

Explanation (requires correct answer)

1. Which of the following changes in the cell prevents it from going through the process of cell suicide?

- A. Avoidance of apoptosis
- B. Changes in metabolism
- C. Limitless replication
- D. Stimulation of angiogenesis
- E. Warburg effect

Explanation (requires correct answer)

2. Which of the following is a proto-oncogene?

- A. *BRCA1*

3. Which of the following inhibits caspases, which effectively stops the process of apoptosis?

A. *BRCA1*

B. *BRCA2*

C. IAPs (inhibitors of apoptosis proteins)

D. p53

E. *RB*

Explanation (requires correct answer)

4. Which of the following terms describes cancerous cells that have additional mutations and are fitter compared with the original cancer cell?

# Cancer Growth and Metastasis

Last updated September 24, 2025  16 min read 

**Author:** ScholarRx

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## Learning Objectives (4)

*After completing this brick, you will be able to:*

- 1 Explain the concepts of tumor cell doubling and growth fraction.
- 2 Describe how tumor cells invade tissues.
- 3 Explain the mechanisms by which tumor cells evade immune detection.
- 4 Describe the three main pathways by which tumor cells metastasize.

## Doubling Time

The doubling time is the amount of time it takes one cell to divide or a group of cells to double in quantity (Figure 1). The doubling time varies from one cancer to another and can vary even between cases of the same type of cancer. The clinical utility of doubling time is to estimate a prognosis based on how fast the tumor doubles in size. This is important because it correlates with the aggressiveness of the tumor. For example, when monitoring a lung nodule, if it was 1 cm in diameter and it grows to 2 cm within 4 years, the doubling time is 4 years. This tumor would not be considered very aggressive. In comparison, if the nodule was 1 cm in diameter and grew to 2 cm within 2 months, the outlook would be very different. This doubling time is 2 months, and the tumor is considerably more aggressive, which would warrant a more aggressive treatment course.

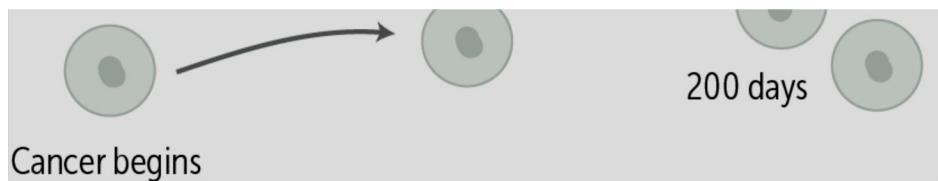


Figure 1

What is the doubling time shown in Figure 1?

## Growth Fraction

The growth fraction is the amount of tumor cells that are within the **proliferative phase** of the cell cycle. Most of our cells are in the resting (nonproliferative) phase, which is G0. During periods of growth, cells leave the resting phase (G0) and enter into G1. The cell will proceed through the interphase (G1, S, G2) and M phase (mitosis, cytokinesis) to ultimately divide into two cells (Figure 2).

## QUIZ

 Tap image for quiz

Figure 2

When the tumor is still in the early stages of growth, the majority of cells are in the proliferative phase. The interphase requires lots of nutrients, which are supplied by blood flow to the tumor. When a tumor grows too large, it outgrows its blood supply and is no longer able to maintain so many cells in the proliferative phase. As the tumor grows larger, more cells leave the proliferative phase and enter G0. This detail is clinically important because the majority of chemotherapy agents target cells in the proliferative phase of the cell cycle.

## Cell Death Rate

There is a natural cycle of old cells dying and being replaced by new ones. This is true in tumors as well. The number of cells that turns over per unit time is known as the cell death rate.

## How Do Subclones Increase Malignant Potential?

So how do some tumors decrease their doubling time and evade the immune system? Over time, some tumors acquire a greater malignant potential. This occurs incrementally. With each cell independently mutating, some mutations can prolong tumor cell survival, and others are detrimental to tumor cell survival.

A **subclone** (also known as a tumor cell variant) describes a tumor cell that has acquired additional mutations. Various tumor subclones will have different effects on growth, invasion, metastasis, and resistance to therapies (Figure 3).

**Figure 3**

Over time, subclones with mutations that portend a survival benefit will accumulate and make up a greater proportion of the tumor. These mutations could inhibit tumor suppressor genes and activate proto-oncogenes. Tumors are initially monoclonal, but by the time they are larger and clinically evident, the cells are heterogenous. Certain subclones undergo immune selection, the highly antigenic subtypes undergo apoptosis, and those that can evade the immune system survive, grow, and invade, leading to metastasis.

What factors determine the rate of tumor growth?

## How Do Cancer Cells Invade Tissues?

A cancer is considered to be *in situ* when it does not penetrate through the underlying basement membrane. The basement membrane is a thin layer of connective tissue that separates the epithelium from the underlying tissue. A cancer becomes invasive when it crosses the basement membrane.

Invasive cancers have the ability to metastasize, or spread to other parts of the body. The steps involved in metastasis are invasion, intravasation, extravasation, and growth at distant organ sites ([Figure 4](#)).

**Figure 4**

To fully understand this process, let's first review the composition of our

To fully understand this process, let's first review the composition of our tissues. Tissues are covered with an outer layer of epithelial cells held together by several proteins. Some proteins that are important in intracellular linkage are E-cadherin and catenins (Figure 5).

Figure 5

### Step 1: Invasion

Invasion begins when cancers separate cells by disrupting the function and integrity of E-cadherin or catenins (Figure 6). For example, malignant breast adenocarcinomas cause the downregulation of E-cadherin within breast tissue, making it easier to separate the cells from one another. This

allows malignant cells to easily move from the primary tumor.

Figure 6

The tumor cells from the primary tumor are now mobile and have the task of invading the basement membrane and extracellular matrix. This is done by cleaving, using proteases. The proteases are secreted from the tumor cells themselves or induced by macrophages or fibroblasts within the surrounding tissues. The release of proteases not only degrades the stroma but also promotes tumor cell growth by releasing growth-promoting agents. Tumor cells migrate in an amoeboid-type pattern, using the actin skeleton and signaling between the tumor and stromal cells to ratchet

through the extracellular matrix.

## Step 2: Intravasation

Intravasation involves entry into the bloodstream or lymphatics. Many circulating tumor cells will die from shear stress from blood or lymphatic flow or apoptosis due to loss of adhesion. Tumor cells bind to each other or to platelets to survive in the bloodstream. They may activate coagulation factors, resulting in emboli. A tumor cell is significantly larger than most blood cells and for this reason will likely get stuck at the first capillary bed it crosses, getting closer to its final destination.

## Step 3: Extravasation

Extravasation is the exit from the bloodstream and into the tissue. Adhesion molecules and anatomic location play a big role. However, some cancers prefer to metastasize to organs that are not nearby. One example of distant metastasis is the predilection of lung cancer to metastasize to the adrenal glands. This may be due to specific adhesion molecules on target endothelium. Tumor cells may express specific ligands (binding molecules) for certain endothelium.

## Step 4: Growth at Secondary Site

Growth at a secondary site can only occur if the surrounding tissue of the target organ is favorable. Metastasis will not occur if the stromal environment is not conducive to the tumor's growth, for example, if certain growth factors are not present. A growing tumor requires certain factors to survive.

What are the four steps of tumor cell metastasis?

## How Does Cancer Evade the Immune System?

As previously noted, as a tumor grows it develops subclones, each with its own unique features. One such feature is immune evasion. Mechanisms for immune evasion include:

- Antigen masking
- Outgrowth of antigen variants
- Loss of major histocompatibility complex (MHC) molecules
- Lack of co-stimulation
- Immunosuppression
- Apoptosis of cytotoxic T cells

### Antigen Masking

Antigen masking is one way that tumor cells hide from the immune

system. Some tumor cells secrete an excess of extracellular matrix material called glycocalyx. This thick coating on cells “masks” the antigens (molecules) on cancer cells, making it more difficult for immune cells to target them for destruction (Figure 7).

Figure 7

## Outgrowth of Antigen Variants

If a subclone of tumor cells is highly immunogenic, meaning it can easily present as foreign to host immune cells, the subclone group will be eliminated. In contrast, some tumor subclones can lose the expression of surface antigen or downregulate antigen expression. These tumor cells will not express an antigen that can be recognized by any of our immune cells. Although this has been observed in cancers such as melanoma, the exact mechanism is unknown (Figure 8).

Figure 8

## Loss of MHC Molecules

In some cases, tumor cells can change their identity to avoid immune system defenses. Cytotoxic T cells are white blood cells that fight infection and work to kill foreign cells and cancer cells. These T cells identify target cells by looking for MHC class I molecules. MHC is a receptor present on all cells that displays antigens on the cell surface. Some tumor subclones undergo mutations to lose the MHC molecules so they are no longer recognized by cytotoxic T cells (Figure 9).

**Figure 9**

## Lack of Co-Stimulation

In general, a T cell can only be activated after receiving two signals; this ensures that T cells are not destroying host cells (Figure 10). The first signal is from antigen activation presented by MHC class I or MHC class II molecules. The second signal is a co-stimulatory signal from the antigen-presenting cell (APC).

**Figure 10**

If this co-stimulatory signal is not received, the T cell will undergo apoptosis, programmed cell death (Figure 11). Tumor cells can rid themselves of this co-stimulatory signal, allowing them to evade the immune system and cause destruction of T cells.

**Figure 11**

## Immunosuppression

The immune response is regulated by cytokines, which are small proteins that function as signaling molecules. One of these cytokines is transforming growth factor  $\beta$  (TGF- $\beta$ ), a potent immunosuppressant capable of suppressing the activities of B cells, T cells, dendritic cells, and macrophages. Some tumor cells secrete TGF- $\beta$  in large quantities, suppressing the immune system (Figure 12).

What potent immunosuppressant do tumor cells use to evade immune system defenses?

## Apoptosis of Cytotoxic T Cells

Apoptosis (programmed cell death) is basically a self-destruct button. This process can occur via two different mechanisms: the intrinsic or extrinsic pathway. Tumor cells such as melanoma and hepatocellular carcinoma express a receptor that leads to apoptosis via the extrinsic pathway. They express FasL, which binds to the Fas-receptor on T cells, leading to apoptosis of cytotoxic T cells.

## What Are the Different Pathways of Metastasis?

There are three main pathways by which tumor cells can metastasize. Tumors can spread lymphatically (through the lymphatic system), hematogenously (through the circulatory system), or by seeding (directly

**Figure 12**

onto nearby structures). In many cases, the route of metastasis is determined by the type of cancer.

Carcinomas, epithelial-derived tumors, are associated with lymphatic spread. Sarcomas are of mesenchymal origin and are associated with hematogenous spread. However, this is not a set rule because the reverse can also occur. Although most carcinomas spread lymphatically, four types are known for spreading hematogenously: follicular thyroid carcinoma, choriocarcinoma, renal cell carcinoma, and hepatocellular carcinoma.

#### Four Carcinomas Route Hematogenously:

- Follicular thyroid carcinoma
- Choriocarcinoma
- Renal cell carcinoma
- Hepatocellular carcinoma

#### Lymphatic Spread

The reason for a tumor cell to intravasate lymphatically is mostly a mechanical issue. The lymphatic pathway is a low-shear system; it does not have the tight junctions and basement membrane associated with blood vessels, making it easier for a tumor cell to get into a lymphatic

vessel than a blood vessel. An example of a tumor that shows lymphatic spread is breast cancer. Lymph node involvement is based off the path of lymphatic drainage. Breast cancers originating from the upper outer quadrants will first travel to axillary lymph nodes (nodes in the arm pits) because the lymphatic drainage is nearby.

#### Hematogenous Spread

Hematogenous spread can occur through arteries or veins. Arteries are thicker and harder to penetrate because of their elastin content, so this is a less common route. With venous spread, tumor cells follow the normal venous drainage pattern and become embedded in the first capillary bed they reach. This helps explain why the liver and lung are the most common sites of hematogenous metastasis. All portal blood from the colon, stomach, and pancreas drains into the liver, which is why many liver metastases are from cancers primary to these three organs. Venous blood from the superior and inferior vena cava flows to the lungs. Metastases to the lung are commonly from cancers of the bladder, colon, breast, and prostate.

#### Seeding

Seeding is another mechanism of cancer spread. We can imagine a process similar to how a gardener sows seeds in an open space of the garden. Cancer seeding occurs in the same fashion, requiring an open space, such as within the peritoneal cavity, pleural cavity, subarachnoid space, or joint cavities. For example, ovarian carcinoma is known for seeding the peritoneal cavity, and glioblastomas use the subarachnoid space to seed within the brain and spinal cord.

By which pathway do carcinomas typically metastasize?

#### CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to TF, what are the likely locations and sources of TF's metastases?

Unfortunately, TF has stage IV breast cancer, with involvement of her lymph nodes and lungs. You now know that breast cancer can spread to the axillary lymph nodes directly and to the lungs via the superior vena cava through the process of intravasation and extravasation. You spend a good deal of time with TF, answering her questions and supporting her through the discussion. After discussing things with her family, TF decides to undergo chemotherapy. You call her on the phone the next day to see how she is doing. "Not bad. Today is better than yesterday. I have a wonderful and supportive family," TF says.

## Summary

- Doubling time is the amount of time it takes a group of cells to double in size; this varies between different types of cancers.
- The growth fraction corresponds to the number of tumor cells within the proliferative phase, which includes any stage of the cell cycle other than G<sub>0</sub>; this indicates that cells are dividing.
- Tumor subclones occur when some of the tumor cells acquire mutations; these mutations can benefit the tumor and lead to immune evasion and eventual metastasis.
- Immune evasion is achieved by antigen masking, outgrowth of antigen variants, loss of MHC molecules, lack of co-stimulation, immunosuppression, and apoptosis of cytotoxic T cells.
- The steps of metastasis are invasion, intravasation, extravasation, and growth at secondary sites.
- Intravasation corresponds to tumor cell invasion through the extracellular matrix, into the bloodstream, and travel to a secondary site.
- In extravasation, tumor cells exit the bloodstream or lymphatics and infiltrate outside of the capillaries.
- Growth of a tumor at a distant site relies on the environment of that tissue; without the proper stromal environment, such as cytokines and growth factors, survival of the tumor cannot occur.
- A tumor can metastasize lymphatically, hematogenously, or by seeding.
- Carcinomas are associated with lymphatic spread.
- Sarcomas are associated with hematogenous spread.
- Seeding occurs within open spaces such as the peritoneal cavity, subarachnoid space, pleural space, and joint cavities.

# Oncogenic Microbes and Their Role in Cancer

Last updated September 25, 2024  18 min read 

Author: ScholarRx

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## Learning Objectives (3)

*After completing this brick, you will be able to:*

- 1 Describe the mechanisms by which oncogenic microorganisms cause cancer.
- 2 List the main cancers associated with oncogenic microorganisms.
- 3 List the main types of oncogenic microorganisms and describe the cell affinities for each.

## CASE CONNECTION

You are seeing RS, a 32-year-old male, in the dermatology clinic during a fourth-year elective. You note multiple, red-violet, raised lesions on his arms. "That's what I'm here for," RS says. "They continue to grow." RS has had no new contacts or exposures. He is receiving antiretroviral therapy for HIV infection. His exam is otherwise unremarkable.

What is the diagnosis? Consider your answer as you read, and we'll revisit RS at the end of the brick.

[GO TO CONCLUSION](#) 

Did you know that some cancers are caused by microorganisms such as viruses, bacteria, and parasites? Viruses are especially well known for causing cancers like [cervical cancer](#), [B-cell lymphomas](#), and [hepatocellular carcinoma](#). In this brick, we will take a look at nine microorganisms, which cells they target, their mechanisms of action, and what cancers they can cause.

### INSTRUCTOR NOTE

There are a lot of details in this brick that are not required at this point. The important take away is to know which viruses, bacteria, etc. are associated with which cancers. Details will follow in other future sessions.

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## Viruses: The Front Runner

That common cold you have had for the last 2 weeks because you were too tired to go to the doctor? Watch out! Just kidding—sort of. The common cold probably will not cause cancer, but 12% of cancers are caused by viruses. Viruses typically target specific cell types. They take over the machinery of the cells and can alter genes. When this occurs, the cell can be turned toward the path of cancer. Let's take a look at a few of the most common oncoviruses (ie, viruses that cause cancer).

### Epstein-Barr Virus

Epstein-Barr virus (EBV), also called human herpesvirus 4 (HHV-4), is best known as the cause of mononucleosis or “mono.” Mononucleosis is often referred to as the “kissing disease” because it is most commonly transmitted by salivary contact during the teenage years. Although mononucleosis itself does not cause cancer, EBV can lead to its development.

How does this happen? EBV targets B lymphocytes. It often remains latent in these cells for a very long time, binding to the CD21 cell marker. With the affinity for this cell type, this virus is more likely to infect these cells and alter their genetic make-up. This action increases the chances for two types of cancers that are associated with B cells: Hodgkin lymphoma and Burkitt lymphoma.

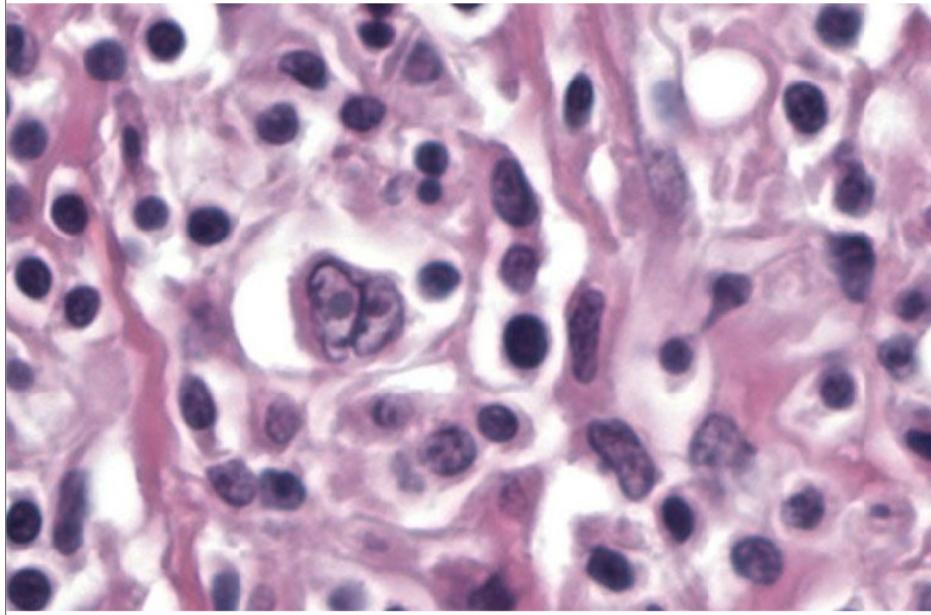
Which cancers are associated with EBV infections?

Hodgkin lymphoma cases are related to infection with EBV about 50% of the time. Risk factors for developing Hodgkin lymphoma include immunosuppression and a family history of the disease. On histology, this cancer is typified by the presence of Reed-Sternberg cells, colloquially referred to as “owl eye” cells because they typically have a bilobed nucleus with prominent eosinophilic inclusion-like nucleoli ([Figure 1](#)).

#### INSTRUCTOR NOTE

We will discuss this further in Lymphomas. For now just know the association between EBV and Hodgkin Lymphoma and Burkitt lymphoma

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### QUIZ

Tap image for quiz

Figure 1

### CLINICAL CORRELATION

An important difference between Hodgkin and non-Hodgkin lymphoma on light microscopy, which can be seen in [Figure 1](#) with an H&E (hematoxylin and eosin) stain, is the presence of Reed-Sternberg cells in the former condition.

Burkitt lymphoma is a type of [non-Hodgkin lymphoma](#). About 75% of cases have a t(8;14) translocation, resulting in translocation of c-MYC and [immunoglobulin heavy-chain locus](#) (IgH), which causes increased constitutive levels of c-MYC. c-MYC signaling helps the cancer cells survive and proliferate. Under a light microscope, neoplastic B lymphocytes of Burkitt lymphoma appear monomorphic and highly mitotically active.

#### LECTUROR NOTE

This will be discussed at a later session. The details of Burkitt lymphoma are not necessary at this point.

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There are three subtypes of Burkitt lymphoma:

- African (endemic) Burkitt lymphoma
- Sporadic (nonendemic) Burkitt lymphoma
- Burkitt lymphoma occurring in patients with [HIV](#) infection

The African subtype is, as the name suggests, endemic to certain parts of Africa. It is virtually always positive for EBV and typically presents in children or young adults as a large mandibular mass ([Figure 2](#)). The sporadic subtype also occurs mainly in children and typically presents with a fast-growing mass involving the ileocecum. EBV is found in only 15% of sporadic cases and 25% of HIV-associated cases.

the regulation of vascular endothelial growth factor, or VEGF. VEGF is primarily involved in angiogenesis, the formation of new blood vessels from preexisting blood vessels. The virus allows for VEGF to activate continuously, resulting in increased angiogenesis. This activity is the cause of the red- and violet-colored lesions characteristic of the disease. The cells that HHV-8 targets for this process are primitive mesenchymal cells. Oncogenesis in mesenchymal cells results in a sarcoma instead of a carcinoma (which originates in epithelial cells). HHV-8 also has some affinity for B cells.

This cancer often afflicts immunosuppressed individuals, especially patients with AIDS. Kaposi sarcoma typically presents as red- and violet-colored lesions on the skin of the extremities (Figure 3).

**Figure 2**

EBV can also cause nasopharyngeal carcinoma. In this case, epithelial cells are the primary target. EBV-associated nasopharyngeal carcinoma is common among adults in Asia and children in Africa. This malignancy resembles squamous cell carcinoma.

## **Human Herpes Virus 8**

Human herpes virus 8 (HHV-8), also known as Kaposi sarcoma–associated herpesvirus, is a herpes virus transmitted by salivary contact. HHV-8 alters

**Figure 3**

In addition to Kaposi sarcoma, HHV-8 is the cause of a B-cell lymphoma known as primary effusion lymphoma. Primary effusion lymphoma is a rare non-Hodgkin lymphoma. HHV-8 is also positive in multicentric Castleman disease and some cases of multiple myeloma.

## Hepatitis Viruses

Hepatitis viruses, specifically hepatitis C (HCV) and hepatitis B (HBV), can cause hepatocellular carcinoma. In both cases, chronic infection results in cirrhosis (ie, fibrosis or scarring in the liver). A significant number of patients with cirrhosis will eventually develop hepatocellular carcinoma. We'll look at each of these viruses individually.

Hepatitis C virus (HCV) is transmitted commonly by IV drug use and occupational exposure, such as a needle stick injury. It is uncommonly transmitted by sex and transplacentally. In the past, HCV was not uncommonly transmitted through blood transfusion or organ transplantation. However, improved screening methods have drastically reduced the incidence of transfusion or transplant-related HCV infection.

The infection causes inflammation of the liver and results in jaundice. About 60%-80% of HCV infections become chronic, which, if you recall, is where the problem begins. The chronic infection causes lymphocytes to accumulate in the liver tissue (this is called hepatitis). Some cases of hepatitis evolve into cirrhosis and eventually into hepatocellular carcinoma (Figure 4).

## QUIZ

 Tap image for quiz

Figure 4

Hepatitis B virus (HBV) is transmitted sexually, through IV drug use, and from mother to child during childbirth. Professionals with an increased risk of being exposed to blood with HBV (eg, health professionals, especially nurses and doctors) are required to get the HBV vaccine. The development of hepatocellular carcinoma from chronic HBV infection has the same pathophysiology as HCV. However, it has another key component. HBV can incorporate some of its DNA into the DNA of a host hepatocyte. This allows the virus to perpetuate, leading to a chronic infection. These changes can cause the development of hepatocellular carcinoma over 11

changes can cause the development of hepatocellular carcinoma as well.

## Human Papillomavirus

Did you have to get the Gardasil shot when you were a teenager? Both females and males ages 9-26 years can receive this shot to “guard” against human papillomavirus (HPV). HPV is a virus that can cause warts and cancer. It comes in several serotypes. HPV serotypes 1 and 4 cause warts in children, known as verruca vulgaris. HPV-6 and HPV-11 can present as genital warts or recurrent respiratory papillomatosis (skin surface elevations in the larynx).

Several HPV serotypes—most notably HPV-16, -18, -31, and -33—are considered “high-risk” serotypes because they frequently are associated with specific types of cancer, most notably cervical carcinoma, but also certain cancers of the vagina, vulva, penis, anus, rectum, and oropharynx. Let’s take a look at how these strains cause this type of cancer.

The key players affected by HPV are the tumor suppressor proteins p53 and Rb (Rb is the retinoblastoma protein encoded by the RB gene). p53 and Rb are crucial regulators of the cell cycle, specifically the transition from the G1 phase to the S phase. G1 is the phase where most of the cell and its components double in size, except for DNA. S is the phase where the DNA “doubles” or a second set is synthesized from the original strands. p53 and Rb inhibit the progression of the cell cycle from the G1 to S phase.

Arresting this process gives the cell time to correct any issues in duplication of cellular components and any problems found in the DNA before the DNA is synthesized in the S phase. HPV stops this process.

How does HPV stop these tumor suppressor genes from performing their function? HPV encodes for two molecules: E6 and E7. E6 has an affinity for and destroys p53. E7 does the same but with Rb. When p53 and Rb are

destroyed, the cell cycle can continue without any checks from the G1 to S phase. This event permits the multiplication of cells with mutations. These mutated cells eventually become cancer.

### INSTRUCTOR NOTE

This will be discussed in Female Reproductive Pathology, year 2. Details are not necessary now except to know that HPV (especially types 16 and 18) is associated with squamous cell carcinoma of the cervix, as well as other types of squamous cell carcinomas to be discussed in the future.

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What is the mechanism of oncogenesis in HPV infection?

## Human T-Cell Leukemia Virus Type 1

Human T-cell leukemia virus type 1 (HTLV-1) is a retrovirus like HIV. The virus is transmitted from mother at birth (most common), sexually, and through IV drug use, direct blood-blood contact, and breast milk. The exposure can occur several decades before clinical features appear.

Infection with HTLV-1 primarily affects the CD4 T cells. HTLV-1 produces several proteins that cause changes in the body; the main focus of this discussion is the Tax oncoprotein. The name Tax (transactivator from the X-gene region) comes from the fact that the gene is located on the pX region of the viral *ENV* gene and is an activator of viral protein transcription.

The Tax oncoprotein stimulates new leukocyte production by increasing molecular signaling (IL-2 and IL-15), which promotes T-cell production. In addition, Tax immortalizes T lymphocytes *in vitro* (ie, T lymphocytes that would typically not proliferate indefinitely are now mutated to continue division). Increased proliferation due to Tax protein activity and immune system response can overwhelm the checks and balances systems of the cell cycle. Without checks and balances, CD4 T lymphocytes develop mutations and increase in numbers, known as lymphocytosis. It may eventually lead to a diagnosis of adult T-cell leukemia/lymphoma.

• TRUCTOR NOTE

Again, the details will be discussed in the Lymphoma session later.  
For now just associate the virus with the disease

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Which cell type is primarily affected by HTLV-1?

## Bacteria

Bacteria are everywhere! No, really, everywhere! That being said, many bacteria work with you rather than against you. Those that don't tend to go to war with the human body. This war causes inflammation, which can irritate nearby cells and cause them to become cancer. One species in particular that likes to cause problems is *Helicobacter pylori*.

*H pylori* is a curved, gram-negative, motile, rod-shaped bacterium. *H pylori* infection is not uncommon; in fact, 50% of the world's population is colonized by this organism. However, if the infection is left untreated and becomes chronic, it increases your risk of gastric adenocarcinoma and a particular type of lymphoma called mucosa-associated lymphoid tissue (MALT) lymphoma.

*H pylori* has multiple virulence factors that allow it to live and colonize in the highly acidic environment of the stomach. The infection induces inflammation, leading to reactive oxygen species, which damage the surrounding cells. In addition, the gastric cells proliferate to create extra layers to protect the underlying mucosa. If the organism is not cleared, the infection becomes chronic.

This constant war between host immunity and *H pylori* transitions the initially developed superficial gastritis to atrophic gastritis (ie, loss of gastric glandular cells and replacement by fibrous tissue). Without successful treatment, the mucosa continues to evolve from the original cell type to a new cell type, known as metaplasia. Then, the new cells exhibit disordered growth, known as dysplasia. If the dysplasia progresses, it may evolve into carcinoma (cancer).

How much of the world's population is colonized by *H pylori*?

## Parasites

Parasites—organisms that rely on other organisms to grow and proliferate—can damage their hosts. Sometimes, parasites cause the host to have an immune reaction, flu-like symptoms, or even blindness. Did you know that parasites also can cause cancer? These parasites are located in the Middle East, Africa, and Asia. Inhabitants of and travelers to these countries are at risk. Two types of flatworms and one helminth are known for causing cancer. We will explore the helminth, *Schistosoma haematobium*.

*S haematobium* is a member of the *Schistosoma* family of parasites. All schistosomes are free-living aquatic parasitic flat worms, also known as helminths. The immature parasite enters the human body via the skin and may present as an itchy skin rash known as “swimmer’s itch.” Then it travels through the bloodstream to the liver, where it matures into the adult phase of its life cycle. It mates with another schistosome, and the eggs exit the body by urine and defecation into the water, where a snail becomes the intermediate host until an immature organism develops and is able to infect another human.

*S haematobium* has an affinity for the bladder, where it causes urinary schistosomiasis (Figure 5).

## Parasites

## QUIZ

 Tap image for quiz

Figure 5

Chronic infection results in pain, secondary infections, kidney damage, and bladder cancer. This process is similar to that described in many other organisms. Infection leads to activation of the host's immune system. Insufficient clearance of the organisms by the immune system results in chronic infection. Cyclical infection and immune system response cause inflammation and the production of substances, such as reactive oxygen species, that damage host tissue. Damaged tissue means increased proliferation of new tissue by the host. This development can spiral into metaplasia, then dysplasia, and then carcinoma if not caught in time.

## Wrapping Up

INSTRUCTOR NOTE

This table is a good reference. There is no need at this point to know about the specific cancers but please understand the associations of the viruses, bacteria, and parasite to the specific cancers mentioned.

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Wow! Viruses, bacteria, and parasites are small but incredibly powerful organisms that are masters of survival. Refer to Table 1 for a quick review of the key points.

Table 1

Microorganism	Cell Affected	Mechanism of Cancer Development	Type of Cancer
<b>Viruses</b>			
EBV	B lymphocytes Squamous cells	Opportunistic	Hodgkin lymphoma Burkitt lymphoma Nasopharyngeal carcinoma
HHV-8	Primitive mesenchymal cells B lymphocytes	Altered regulation of VEGF	Kaposi sarcoma Primary effusion lymphoma Multicentric Castleman disease and some multiple myeloma
HBV/HCV	Hepatocytes	Chronic inflammation HBV DNA integration	Hepatocellular carcinoma

			into hepatocyte
HPV	Squamous cells	E6 inactivates p53 E7 inactivates Rb	Cancers of the cervix, vagina, vulva, penis, anus, rectum, and oropharynx
HTLV-1	CD4 T cells	Tax protein	Adult T-cell leukemia/ lymphoma
<b>Bacteria</b>			
<i>H pylori</i>	Gastric epithelial cells  Lymphocytes in mucosa-associated lymphoid tissue	Chronic inflammation	Gastric adenocarcinoma  Lymphoma
<b>Parasites</b>			
<i>S haematobium</i>	Bladder epithelial cells	Chronic inflammation	Bladder carcinoma

### CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to RS, what is his diagnosis?

RS has Kaposi sarcoma due to HHV-8. HHV-8 allows for continuous activation of VEGF, resulting in an increase in the formation of blood vessels. These new blood vessels bring nutrients to the skin, which is responsible for the physical appearance of the lesion. RS responds to the treatment for his Kaposi sarcoma and continues taking his multidrug regimen to treat his HIV infection.

## Summary

- Viruses, bacteria, and parasites can cause cancer.
- Each of these microorganisms has a specific affinity for a certain cell type.
- The microorganisms have unique mechanisms of action to infect the human host and initiate the development of cancer.
- Viruses cause 12% of all cancers.
- EBV can cause Hodgkin lymphoma, Burkitt lymphoma, and nasopharyngeal carcinoma because of its affinity for B cells.
- HHV-8 causes Kaposi sarcoma and primary effusion lymphoma because of its deregulatory effects on VEGF.
- HBV and HCV target hepatocytes and cause hepatocellular carcinoma.
- HPV uses E6 and E7 to inhibit p53 and Rb, respectively, causing anogenital carcinomas, especially cervical cancer.
- HTLV-1 uses the Tax protein to mutate CD-4 T cells, resulting in adult T-cell leukemia/lymphoma.
- The main cancer-causing bacteria is *H pylori*, which is associated with gastric adenocarcinoma and MALT lymphoma.
- Parasites, like bacteria, cause chronic inflammation and can lead to cancer, such as bladder carcinoma from *S haematobium*.

## Review Questions

1. A 13-year-old child presents to you with a large tumor on his jaw. He and his family recently emigrated from Uganda in the hopes of finding him better care. What organism most likely caused this child's tumor?
  - EBV
  - H pylori*

# Paraneoplastic Syndromes

Last updated November 9, 2023  18 min read 

**Author:** ScholarRx

[Listen to this Brick](#)

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## Learning Objectives (4)

*After completing this brick, you will be able to:*

- 1 Describe the main paraneoplastic syndromes affecting the skin and musculoskeletal system.
- 2 Describe the main paraneoplastic syndromes affecting the endocrine system.
- 3 Describe the main paraneoplastic syndromes affecting the central and peripheral nervous systems.
- 4 Define paraneoplastic syndromes, and explain how they are different from the direct, local effects of a tumor.

Usually the signs and symptoms—things like peripheral neuropathy or delusions or kidney stones—would not immediately make you think “cancer.” But they result from some action on the part of the tumor cells, such as secretion of hormone-like substances or stimulation of an aberrant immune response.

Paraneoplastic syndromes are estimated to occur in up to 20% of patients with cancer. Some paraneoplastic syndromes are characteristic of a specific type of cancer, while others can occur in several different types of cancer. As you might expect, paraneoplastic syndromes can cause a wide variety of symptoms in just about every organ and organ system in the body. Some of the most commonly affected organs and organ systems are the nervous system, endocrine system, skin, and musculoskeletal system. In this brick, we'll focus on the most common and most notable paraneoplastic syndromes in each of these categories.

## Paraneoplastic Syndromes That Affect the Nervous System

Paraneoplastic syndromes affecting the nervous system almost exclusively result from immune responses to malignancy (ie, immunologic cross-reactivity between components of the nervous system and tumor cells). Paraneoplastic neurologic syndromes are often detected before an actual cancer diagnosis. Therefore, identifying a neurologic paraneoplastic syndrome is often the first clue to an underlying malignancy.

Two common and important paraneoplastic syndromes that affect the nervous system are covered in detail in other bricks, but they deserve brief mention here. They are myasthenia gravis and Lambert-Eaton myasthenic syndrome (LEMS). Myasthenia gravis affects postsynaptic acetylcholine

receptors and is characterized by muscle weakness that worsens as the affected muscle is used. When it occurs as a paraneoplastic syndrome, the most common underlying tumor is thymoma. LEMS affects presynaptic calcium channels and causes muscle weakness that improves as the muscle is used. It is most commonly associated with small cell lung cancer (SCLC).

### Anti-NMDA Receptor Encephalitis

Anti-NMDA receptor encephalitis (ANRE) is brain inflammation (encephalitis) due to autoantibodies to NMDA (*N*-methyl-D-aspartate) receptors in the brain, resulting in a characteristic neuropsychiatric syndrome. The tumor most commonly associated with ANRE is ovarian teratoma.

The signs and symptoms of ANRE are highly characteristic. Patients will often first have headaches, fever, or flu-like symptoms, followed by a predictable and progressive set of neuropsychiatric symptoms that begin a few days later:

- The first phase is dominated by psychiatric symptoms such as anxiety, agitation, paranoia, delusions, hallucinations, mania, unstable mood, cognitive deterioration, abnormal speech, and insomnia, along with behavior and personality changes. Seizures are most common during this phase.
- The second phase follows the first by about a week and is characterized by decreased consciousness, catatonia, and other neurologic symptoms. These include abnormal movements of the face and extremities as well as autonomic instability, seen as tachycardia or bradycardia, hypotension or hypertension, hypoventilation, and hyperthermia. Seizures and insomnia are seen in this stage as well.

ANRE itself can be lethal if not treated. Immediate treatment includes

~~Limbic encephalitis can be fatal if not treated. Immediate treatment includes steroids, intravenous immunoglobulins (IVIG), plasmapheresis, and supportive measures.~~ The offending tumor should be resected as soon as possible. Even with appropriate treatment, cognitive deficits, sleep disturbances, and behavioral abnormalities can persist for years.

What tumor is most commonly associated with anti-NMDA receptor encephalitis?

## Limbic Encephalitis

Limbic encephalitis is an immune-mediated paraneoplastic syndrome that is characterized by inflammation of the structures that compose the limbic system. The typical presentation involves subacute onset of symptoms classically associated with the limbic system. These include short-term memory loss (a hallmark symptom), seizures, personality changes, olfactory and gustatory hallucinations, headaches, agitation, and sleep disturbance.

### CLINICAL CORRELATION

Recall that the hippocampus, amygdala, cingulate gyrus, and mammillary bodies are components of the limbic system. The limbic system is responsible for the famous five Fs: feeding, fleeing, fighting, feeling, and sex.

The cancer most commonly associated with limbic encephalitis is SCLC. The underlying mechanism involves an autoimmune attack targeted at neurons in the limbic system. Antibodies against a neuronal antigen called Hu (anti-Hu antibodies) play an important role in this mechanism. While treatment of the underlying cancer is of primary importance, if symptoms are particularly troublesome, immunosuppressive treatment may provide some relief.

Which cancer is most commonly associated with limbic encephalitis?

## Paraneoplastic Syndromes That Affect the Endocrine System

Tumors sometimes do strange things for reasons that aren't entirely clear. One of these strange activities is hormone secretion (by tumors that have no business making hormones). We're not talking about a thyroid cancer secreting thyroid hormones. That makes sense. But a squamous cell lung cancer that makes parathyroid hormone? That's just strange. To be fair, these "hormones" are often not structurally identical to their normal counterparts (so we often call them hormone-like substances). But they're similar enough to the normal hormones that the body reacts to them as if they were real hormones, and patients end up with all kinds of hormone-related symptoms, sometimes well before the cancer itself makes an appearance.

It's important to note that in these hormone-related paraneoplastic syndromes, the tumor cells are just sitting there making hormone on their own, and they don't respond to any outside signals telling them to stop. This type of secretion is called ectopic, meaning that it's outside of the normal axis of hormonal control.

Normal hormone secretion is responsive to inhibiting signals. When the serum calcium level is low, the parathyroids release parathyroid hormone (PTH); when the serum calcium level reaches normal levels, PTH is no longer released. Ectopic hormone secretion is unresponsive to inhibiting signals. When a tumor cell secretes a PTH-like substance, it doesn't care about the serum calcium level! The serum calcium can be markedly elevated, and the tumor cell will keep on secreting its PTH-like substance.

There are many paraneoplastic syndromes involving the endocrine system.

Here, we'll touch on Cushing syndrome, but because of its importance and breadth, it will be covered in more depth in another brick. Then we'll focus on two of the more common syndromes: hypercalcemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Once you understand how these syndromes work, you can apply that knowledge to any of the other hormone-related paraneoplastic syndromes you may encounter.

### Cushing Syndrome

Cushing syndrome is a common disorder caused by high levels of serum cortisol. Patients develop characteristic signs and symptoms such as deposition of adipose tissue in the upper back and neck region ("buffalo hump") and around the face ("moon facies") along with a number of metabolic derangements, including hyperglycemia.

Although there are other, more common, causes of Cushing syndrome, a small but significant number of cases are caused by a paraneoplastic syndrome. The most common culprit is SCLC, which can secrete a substance so similar to adrenocorticotrophic hormone (ACTH) that it acts just like ACTH and stimulates the production of cortisol by the adrenal gland.

### Hypercalcemia

There are many causes of hypercalcemia (serum calcium >10.2 mg/dL). When a patient is found to have hypercalcemia on a routine laboratory assay but has no clinical signs or symptoms of hypercalcemia, the most common cause is a primary hyperparathyroidism (something in the parathyroid gland itself is causing excess PTH secretion). When patients with hypercalcemia are symptomatic however that's a different story. the

With hypercalcemia are symptomatic, however, that's a different story, the most common cause of symptomatic hypercalcemia is malignancy.

Hypercalcemia is one of the most common paraneoplastic syndromes. Most malignant tumors that cause hypercalcemia do so by secreting a substance called parathyroid hormone-related protein (PTHrP), which, like normal PTH, causes the serum calcium level to increase. A number of cancers are highly associated with the production of PTHrP: most commonly squamous cell carcinoma of the lung and head and neck as well as carcinomas of the breast, ovaries, bladder, and kidneys.

Malignant tumors can also cause hypercalcemia by secreting calcitriol (the active form of vitamin D), which raises serum calcium by several different mechanisms. This is a much less common mechanism of paraneoplastic hypercalcemia, and it's seen primarily in patients with lymphoma.

What cancers are associated with paraneoplastic hypercalcemia?

#### CLINICAL CORRELATION

Recall that parathyroid hormone ultimately increases serum calcium levels and lowers serum phosphate levels. Vitamin D3 (calcitriol) ultimately increases both serum calcium and serum phosphate.

Recall that squamous cell carcinoma of the lung and SCLC are strongly associated with smoking.

Hypercalcemia can present with a variety of signs and symptoms, and key symptoms can be remembered by organ system.

To recall the key symptoms of hypercalcemia: stones, bones, groans, and psychiatric overtones.

Renal: kidney stones, polyuria, nocturia (urinating excessively at night, usually disturbing sleep), dehydration.

Musculoskeletal: Bone pain and muscle weakness.

Gastrointestinal (GI): constipation, GI upset, nausea, vomiting.

Neuropsychiatric: depression, confusion, lethargy, fatigue.

When hypercalcemia occurs as part of a paraneoplastic syndrome, calcium levels can increase to dangerously high levels. In these cases, managing the calcium level is the first priority: a search for the cause can be

the calcium level is the first priority, a search for the cause can be undertaken once the patient is stable.

## Syndrome of Inappropriate Antidiuretic Hormone

As its name implies, the paraneoplastic syndrome of inappropriate antidiuretic hormone (SIADH) results from increased levels of antidiuretic hormone (ADH) because of ectopic production by a tumor. SCLC is by far the most commonly associated cancer. ADH normally stimulates the reabsorption of water in the collecting ducts of kidney, and its action is tightly controlled by physiologic feedback mechanisms. In SIADH, however, the offending tumor releases ADH in an unregulated fashion. This excess ADH causes hyponatremia (decreased serum sodium, <135 mEq/L) through a dilutional effect in the serum and by increasing sodium excretion.

Watch for neurologic symptoms: decreased consciousness, malaise, weakness, seizures, headaches, and memory impairment. Laboratory studies will show hyponatremia, hypo-osmolality (<275 mOsm/kg), and urine that is less dilute than expected (>100 mOsm/kg).

What cancer is most commonly associated with paraneoplastic SIADH?

The immediate management of SIADH is centered on correcting serum sodium levels mainly through fluid restriction and pharmacologic intervention. As with all the paraneoplastic syndromes, the optimal treatment addresses the underlying tumor.

## Paraneoplastic Syndromes That Affect the Skin and Musculoskeletal System

Paraneoplastic syndromes that affect the skin often precede a diagnosis of cancer and are often the first symptoms of an underlying malignancy.

### Acanthosis Nigricans

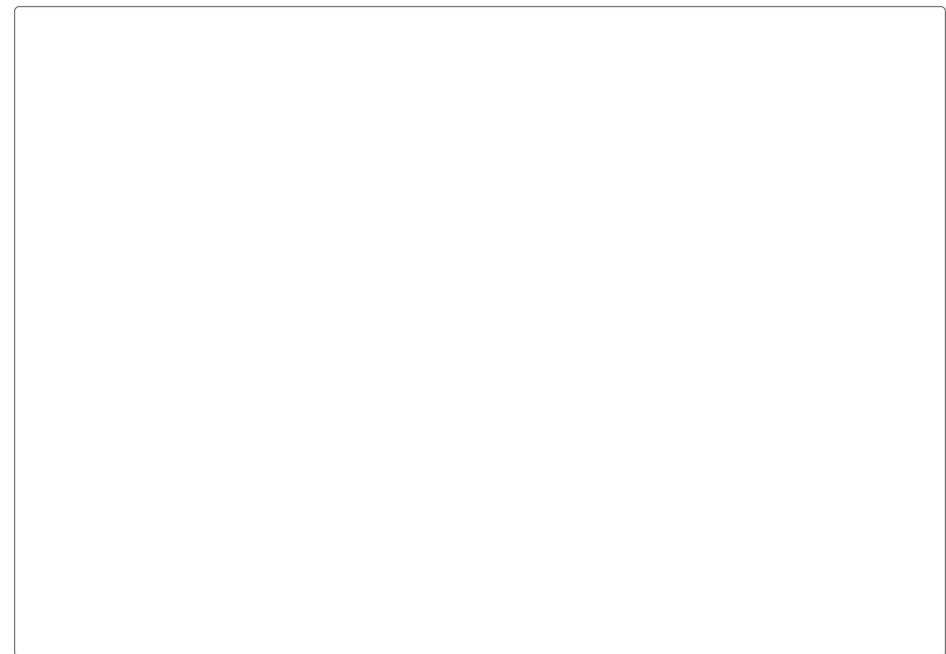
• TRUCTOR NOTE

Will be discussed further in Skin pathology sessions

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Acanthosis nigricans (AN) refers to thickened, black or brown hyperpigmentation of the skin that often has a velvety texture, seen here on the neck ([Figure 1](#)) and axilla ([Figure 2](#)), the most common sites. Most cases of acanthosis nigricans are associated with conditions such as

obesity or diabetes. An estimated 20% of cases, however, are related to an underlying tumor, most commonly gastric adenocarcinoma. It is thought that tumors with this type of paraneoplastic syndrome secrete growth factors that stimulate the formation of the characteristic skin lesions of acanthosis nigricans.



**QUIZ**

 Tap image for quiz

**Figure 1**



**QUIZ**

 Tap image for quiz

**Figure 2**

### Sign of Leser-Trélat

 EDITOR'S NOTE

Will be discussed further in skin pathology sessions.

MARIA PLUMMER

Leser-Trélat sign is the sudden, explosive appearance of numerous seborrheic keratoses ([Figure 3](#)). Seborrheic keratoses are gray-brown, flat-topped, velvety lesions having a “stuck-on” appearance. They are commonly seen in middle-aged and elderly patients, but they typically appear slowly over time. When they appear suddenly, and in large numbers, a search for an underlying malignancy is warranted. The most common cancers with this paraneoplastic syndrome are those involving the gastrointestinal tract. These tumors secrete a substance called transforming growth factor  $\alpha$ , which stimulates keratinocytes and may lead to the development of seborrheic keratoses.

[Figure 3](#)

## Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy is a syndrome of digital-clubbing ([Figure 4](#)), joint swelling and synovial effusions, and joint pain (especially in the large joints). Ninety percent of cases are paraneoplastic.

[Figure 4](#)

Lung cancer (of any type) is the most commonly associated malignancy. The presence of sudden-onset digital clubbing should always prompt a work-up for an underlying malignancy. The mechanism for hypertrophic osteoarthropathy is abnormal skin proliferation and subperiosteal bone formation along the shafts of the phalanges. There is also periostosis (excessive bone formation) and periostitis (inflammation of the periosteum, the membrane that envelopes bone) of tubular bones.

## Wrapping Up

Paraneoplastic syndromes, as we've seen, are characterized by a wide range of different signs and symptoms. Their underlying mechanisms are likewise very diverse. Let's take a step back and summarize what we've covered. We discussed several different paraneoplastic syndromes, grouping them together by the organ system in which most of their symptoms occur. **Table 1** summarizes the presentation, mechanism, and most commonly associated cancers for the main paraneoplastic syndromes discussed in this brick.

**Table 1**

Syndrome	Presentation	Mechanism	Most Commonly Associated Cancers
<b>Neuromuscular</b>			
Anti-NMDA receptor	Phase 1: seizures and psychiatric disturbances. Phase 2: NMDA receptors in the brain.	Antibodies against NMDA receptors in the brain.	Ovarian teratoma

encephalitis	disturbances. Phase 2: dyskinesia, stupor, autonomic instability.	NMDA receptors in the central nervous system	Ovarian teratoma
Limbic encephalitis	Memory loss, seizure, olfactory/gustatory hallucinations, personality changes	Antibodies against Hu antigens in neurons	Small cell lung carcinoma
<b>Endocrine</b>			
Cushing syndrome	Buffalo hump, moon facies, hyperglycemia	Production of ACTH by tumor cells	Small cell lung carcinoma
Hypercalcemia	"Stones, bones, groans, and psychiatric overtones." Very high serum calcium.	Production of PTHrP or calcitriol by tumor cells	PTHRP: Squamous cell carcinomas of the lung, head, and neck; carcinomas of the breast, ovary, kidney, and bladder. Calcitriol: lymphomas.
SIADH	Decreased consciousness, memory impairment, seizures, malaise, weakness, headaches	Production of ADH by tumor cells	Small cell lung carcinoma
<b>Musculocutaneous</b>			
Acanthosis nigricans	Velvety hyperpigmentation of skin	Unclear, tumor secretion of growth factors	Gastric adenocarcinoma
Sign of Leser-Trélat	Abrupt eruptions of multiple seborrheic keratoses	Unclear, tumor secretion of growth factors	Gastrointestinal adenocarcinoma
Hypertrophic osteoarthropathy	Digital clubbing, synovial effusions, joint pain	Subperiosteal bone proliferation, periostosis of long bones	Lung cancer (all types)

## CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to AH, what is the diagnosis? What is the etiology of the elevated calcium level?

You suspect that AH has squamous cell carcinoma of the lung due to his tobacco use and that the hypercalcemia is due to ectopic production of PTH. You admit AH to the hospital, begin antibiotics for his pneumonia, and administer IV fluids as initial management of his hypercalcemia. “We have a few problems here,” you explain to AH. “You have pneumonia, but more seriously, you have a lung mass that I think is cancer. Your symptoms are related to an elevated calcium level that can be associated with certain lung cancers. Once the pneumonia is treated, we’ll be able to address these issues more thoroughly.”

## Summary

- Paraneoplastic syndromes are groups of signs and symptoms that happen in patients with cancer but are not directly related to the growth of the tumor itself.
- There are many such syndromes, some of which can be fatal if not treated.
- Paraneoplastic syndromes often result from immune cross-reactivity or production of hormone by the tumor cells.
- Paraneoplastic neurologic syndromes include anti-NMDA receptor encephalitis, limbic encephalitis, Lambert-Eaton myasthenic syndrome, and myasthenia gravis. Each of these syndromes is associated with specific cancers.

- Paraneoplastic endocrine syndromes result from the secretion of hormone-like substances by tumor cells. Examples include Cushing syndrome, hypercalcemia, and SIADH.
- Paraneoplastic syndromes that affect the skin include acanthosis nigricans and the sign of Leser-Trélat. Both are associated with GI adenocarcinomas.
- Some paraneoplastic syndromes, such as SIADH, require specific, urgent treatment. Overall, however, the focus of treatment is the underlying malignancy.

## Review Questions

1. A 20-year-old female is brought to the emergency department by her roommate. The roommate says the patient has been acting bizarre lately, and she is afraid her friend might be taking psychedelic drugs. She also mentions that over the last few days, the patient had what she thought was the flu. The patient is admitted to the hospital, and a week later her blood pressure becomes unstable, she spikes a fever, and she becomes obtunded. Assuming this constellation of symptoms is all attributable to one underlying cancer, what malignancy would you be most concerned for?

- A. Gastric adenocarcinoma
- B. Lymphoma
- C. Ovarian teratoma
- D. Small cell lung cancer