

# Cancer: Foundations and Frameworks

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**Author:** ScholarRx

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## [Learning Objectives \(3\)](#)

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

- 1 Define metaplasia and dysplasia, and explain the clinical significance of both.
- 2 Explain the concept of tumor cell differentiation, and define anaplasia.
- 3 Describe the main difference between benign and malignant tumors.

We use the word to describe only neoplastic masses of tissue. In this block, we'll use the terms tumor and neoplasm interchangeably.

What does the term neoplasm describe?

## What's the Difference Between Benign and Malignant Tumors?

There are two kinds of tumors:

- Benign tumors do not have the ability to metastasize (spread) to other tissues. In general, benign tumors tend to be smaller and grow more slowly than malignant tumors. Benign tumors are usually surrounded by a capsule, making them more surgically removable and leading to a better prognosis.
- Malignant tumors (cancerous tumors) are those that can invade tissues or spread to other parts of the body. The potential for metastasis is a characteristic feature of a malignant tumor. Malignant tumors usually ~~do not have a capsule and often have a worse prognosis~~.

~~do not have a capsule and often have a worse prognosis.~~

These are generalizations, but the core defining feature of a malignant tumor is that it can metastasize, while benign tumors do not metastasize. However, just because benign tumors do not metastasize, that does not mean that they cannot be life-threatening. For example, a meningioma is a benign tumor of the meninges that can compress brain tissue and cause neurological problems such as seizures, paralysis, and changes in vision. Benign brain tumors in particular are dangerous because of the limited space in the skull.

Table 1 summarizes tumor terminology.

Table 1

Term	Definition
Neoplasm/tumor	A new and abnormal growth of tissue in the body
Invasion	Local growth of a tumor into surrounding tissue
Metastasis	Spread of a tumor to distant sites in the body
Benign	Describes a localized tumor that does not metastasize
Malignant	Describes a tumor that may metastasize; may be resistant to treatment and recur after removal

How can a benign tumor be harmful?

## What Is Tumor Differentiation?

The term “tumor differentiation” has a very specific meaning that might seem a little counterintuitive at first. Let’s start with some definitions, and then we’ll clear up some common misconceptions.

The differentiation of a tumor refers to the degree to which the tumor cells resemble their normal cell counterparts (the cells from which they originated). Well-differentiated tumors are composed of cells that look very much like their cell of origin. Poorly differentiated tumors are composed of cells that bear very little resemblance to their cell of origin.

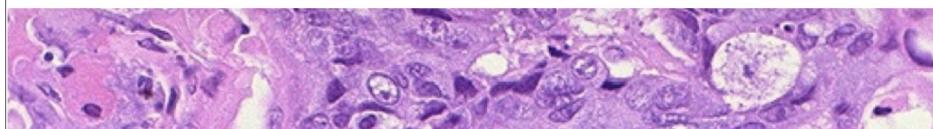
Figure 1 shows a well-differentiated squamous cell carcinoma. The tumor cells are polygonal and have a lot of eosinophilic cytoplasm, like normal squamous cells. There’s a little piece of normal stratified squamous epithelium in this biopsy specimen that you can use for comparison.

### QUIZ

 Tap image for quiz

Figure 1

Figure 2 shows a poorly differentiated squamous cell carcinoma composed of cells that show very little resemblance to normal squamous cells. Like most poorly differentiated tumors, the cells in this image are pleomorphic (vary in size and shape), with hyperchromatic (dark-staining) nuclei and an increased nuclear-to-cytoplasmic ratio.



### QUIZ

Tap image for quiz

Figure 2

Our use of “differentiation” here might seem a little backwards at first. After all, wouldn’t well-differentiated tumor cells look significantly different from their cell of origin?

This is such a common point of confusion that it’s worth spending a little time on it. Using “differentiation” this way when we’re talking about tumors has to do with the way we use that word to describe normal (non-neoplastic) cells. When we’re talking about normal cells, differentiation refers to the presence of unique, characteristic features in a particular type of cell.

Take red blood cells (RBCs), for example. At their youngest, RBCs are virtually indistinguishable from other very early hematopoietic cell precursors. But as they mature, these cells learn how to make hemoglobin,

and they develop an unusual cytoskeletal structure that gives the cell its characteristic biconcave disc shape. This process of acquiring the characteristics of a mature cell is called differentiation. Very young RBCs are said to appear undifferentiated, and mature RBCs are differentiated.

With that in mind, it makes a little more sense to use well-differentiated to describe a tumor that looks very much like its tissue of origin and poorly differentiated to describe tumor cells that seem to have none of the characteristic features of their normal counterpart cells.

### Clinical Implications

Why do we care whether a tumor is well-differentiated or poorly differentiated? In general, poorly differentiated tumors are more aggressive and have a worse prognosis compared with well-differentiated tumors. This is an important characteristic that can be identified by pathologists and is critical in the grading of tumors.

An **anaplastic tumor** does not resemble its tissue of origin at all. The cells have none of the characteristics of their normal counterparts, and it’s impossible to tell what types of cells they are just by looking at them. Anaplastic tumors are composed of undifferentiated cells (cells that don’t show any characteristics pointing toward a particular cell type). On the differentiation spectrum, anaplastic tumors are at the extreme far end, past poorly differentiated tumors.

Anaplastic tumors tend to be composed of cells that are very strange looking (they may be gigantic, contain multiple nuclei, or have huge nucleoli). These odd-looking cells are often called anaplastic. If you never learned the true definition of the term, you might think that anaplastic just means bizarre-looking, and this of course is not the case.

In general, benign tumors tend to be well-differentiated, and malignant tumors can be anywhere on the spectrum of differentiation (from well-differentiated to anaplastic). It is important to know where a malignant tumor falls on the spectrum because well-differentiated malignant tumors tend to have a better prognosis than poorly differentiated or anaplastic malignant tumors.

#### CLINICAL CORRELATION

Tumor grading is a useful histological tool that incorporates the degree of differentiation of a cancer, among other things. There are specific grading systems for specific cancers, such as the Gleason grading for prostate cancer. Note that tumor grading is not the same as cancer staging. The grade of a tumor refers to the way a tumor looks under the microscope, and the stage of a tumor refers to its size and the degree to which it has spread (metastasized).

#### INSTRUCTOR NOTE

Very important concept

MARIA PLUMMER

What are three histological characteristics of poorly differentiated tumor cells?

## What Is Metaplasia?

#### INSTRUCTOR NOTE

This is a review from the Cellular Adaptation session

MARIA PLUMMER

The term metaplasia is based on the Greek word *metaplassein*, which means to mold into a new form. Metaplasia refers to the replacement of one cell type by another, for example, the replacement of squamous epithelium with columnar epithelium ([Figure 3](#)). It's important to note that the cells don't actually change from one type to another. Instead, the change occurs at the stem cell level; instead of producing the normal cell type, the stem cells start producing cells of a different type. Metaplasia

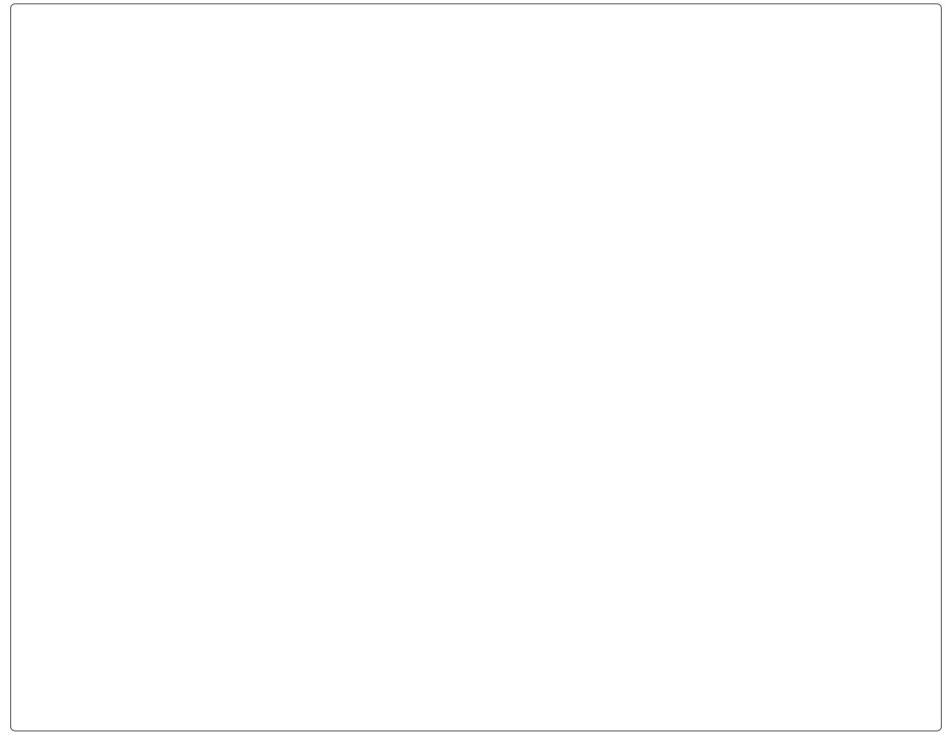
often occurs as an adaptive change in response to repeated or chronic cell stress. Typically, it is reversible, meaning that if the stressor is removed, the cells can revert back to their original type.

**Figure 3**

Two classic examples of metaplasia are airway epithelial metaplasia and Barrett esophagus. In airway epithelial metaplasia, the pseudostratified columnar epithelium of the airways undergoes squamous metaplasia in response to irritants such as cigarette smoke.

In Barrett esophagus, the squamous epithelium of the esophagus is damaged by chronic gastric exposure from acid reflux. Over time, the esophageal squamous epithelium is replaced by columnar epithelium, which secretes protective mucus as a compensatory measure. [Figure 4](#)

shows both normal esophageal squamous epithelium and the metaplasia with goblet cells in the glandular epithelium. While initially reversible, a small number of cases of Barrett esophagus can develop into esophageal adenocarcinoma if untreated.



**QUIZ**

 Tap image for quiz

**Figure 4**

## What Is Dysplasia?

The word dysplasia literally means disordered (dys) growth or formation (plasis). Dysplastic cells look abnormal. They can show various types of morphologic changes, including:

- Pleomorphism
- Hyperchromatic nuclei
- Irregularly shaped nuclei
- High nuclear-to-cytoplasmic ratio
- Loss of polarity (lack of distinction between the top and bottom of the cell)
- Disorderly architecture (for example, cells piling on top of each other instead of sitting in a neat row)

Why do we pay attention to dysplastic changes in non-neoplastic cells? Because dysplasia often precedes cancer. In cancers of epithelial tissue (squamous cell carcinoma and adenocarcinoma), cells often show dysplastic changes long before they turn into cancer cells.

There is a spectrum of dysplasia: mild, moderate, and severe. Let's take a look at an example. [Figure 5](#) shows a section of stratified squamous epithelium from a cervical biopsy. The epithelium on the far left is normal in appearance, but the remaining epithelium shows varying degrees of dysplasia. The mildly dysplastic region contains a few large cells with hyperchromatic nuclei but otherwise looks quite similar to normal epithelium. The severely dysplastic region, however, has lost all architectural structure; the cells are pleomorphic and show no polarity.

### QUIZ

 Tap image for quiz

[Figure 5](#)

Why does it matter how “bad” the dysplasia is? Because the degree of dysplasia is directly correlated with the likelihood of developing cancer. Sometimes, dysplasia disappears and the cell reverts to normal, never progressing to become cancerous. This is especially true for cells that are mildly dysplastic. However, once dysplastic changes become severe, chances are very high that cancer will follow.

The Papanicolaou (Pap) smear is based on the fact that dysplasia precedes cancer. Cells from the cervix are removed with a swab and examined under the microscope for dysplastic changes. If severe dysplasia is present, the patient can undergo a separate procedure to remove the dysplastic epithelium, preventing cancer from developing.

There is a stage after severe dysplasia called carcinoma in situ (CIS). In situ is Latin, meaning in its original place. In CIS, the cells are cancerous, but

They are pre-invasive: they have not broken through their basement membrane and penetrated the underlying tissue. CIS is the very earliest stage of cancer, also referred to as stage 0. Removal of a cancer at this stage is curative because the tumor has not metastasized.

STRUCTOR NOTE

This is an important concept

MARIA PLUMMER

How does metaplasia differ from dysplasia?

 CASE CONNECTION

Thinking back to TF, how do you explain these results to her?

[BACK TO INTRODUCTION ↑](#)

Your intent is to reassure TF quickly so you say, "It's benign." She responds, "I have no idea what that means. Is it cancer?" You explain that a uterine fibroid is the growth of uterine muscle but that it is not cancer. "Benign means that the growth is localized, in your case the growth of uterine smooth muscle cells, and that it will not spread or metastasize to other parts of the body." You explain that the fibroid can be removed for symptoms. Because of persistent pain and bleeding, TF opts for surgery, which she tolerates well without postoperative complications.

## Summary

- The defining feature of a malignant tumor is its ability to metastasize, or spread to the rest of the body.
- Tumors range from well-differentiated to poorly differentiated to anaplastic.
- Well-differentiated tumors tend to grow slowly and have a better prognosis than poorly differentiated tumors.
- Histologic features of poorly differentiated tumors include pleomorphism, hyperchromatic nuclei, and a high nuclear-to-cytoplasmic ratio.
- Metaplasia is the replacement of one cell type by another.
- Metaplasia is often an adaption to some type of chronic damage to tissue, such as in Barrett esophagus.
- Dysplasia is the disordered growth of non-neoplastic epithelial cells characterized by morphologic changes such as pleomorphism and hyperchromatic nuclei.
- Both metaplasia and dysplasia are reversible but in some cases precede cancer.

# Tumor Nomenclature

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**Author:** ScholarRx

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## Learning Objectives (4)

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

- 1 Define neoplasia, and describe the principles of naming tumors according to tissue of origin.
- 2 Explain how benign tumors are named, give examples, and list common exceptions.
- 3 Explain how malignant tumors are named, give examples, and list common exceptions.
- 4 List examples of lesions that sound like neoplasms but are not.

Neoplasms can be benign or malignant. Benign tumors remain localized and do not metastasize (do not invade or spread to other sites in the body). Malignant tumors, on the other hand, are capable of metastasizing. The word “cancer” refers specifically to a malignant tumor.

### What is the main difference between a benign and malignant tumor?

Beyond the difference in their ability to metastasize, certain features are common to each type of tumor. Benign tumors are usually well-differentiated (composed of cells that look very similar to their normal cell of origin), have little mitotic activity, and do not contain areas of necrosis. They also usually have well-demarcated (easy to identify) borders and are often surrounded by a capsule of fibrous tissue. They do not invade surrounding tissues but simply grow larger, “pushing” the adjacent tissue aside.

In contrast, malignant tumors may be anywhere on the differentiation spectrum (from poorly differentiated to well-differentiated). They often

spectrum (from poorly differentiated to well-differentiated). They often show high mitotic activity and contain areas of necrosis (dead cells). They are not encapsulated, and they typically grow in an invasive fashion, extending into the surrounding tissue and running over everything in their path.

#### CLINICAL CORRELATION

Remember the difference between necrosis and apoptosis. Apoptosis is energy-dependent programmed cell death without significant inflammation. Necrosis, on the other hand, is cell death via enzymatic degradation and protein denaturation due to exogenous injury, and it often elicits an inflammatory response.

Benign tumors are typically easily treated. Unless they occur in inaccessible areas (such as deep in the brain), surgical resection is usually curative. Malignant tumors are more difficult to treat successfully. Because of their invasiveness and metastatic potential, surgical excision may not be curative, and chemotherapy and radiation may be required. If a malignant tumor is caught at an early stage, treatment may be effective. Unfortunately, in many cases, the tumor has already spread by the time it is diagnosed, and treatment is less successful.

## How Are Tumors Named?

In general, tumor names have two parts:

- The first part refers to the tumor's tissue of origin

- The first part refers to the tumor's tissue of origin.
- The second part includes the suffix -oma.

Malignant tumors have an added naming convention we'll look at shortly, and there are some exceptions to these naming rules.

## Benign Tumors

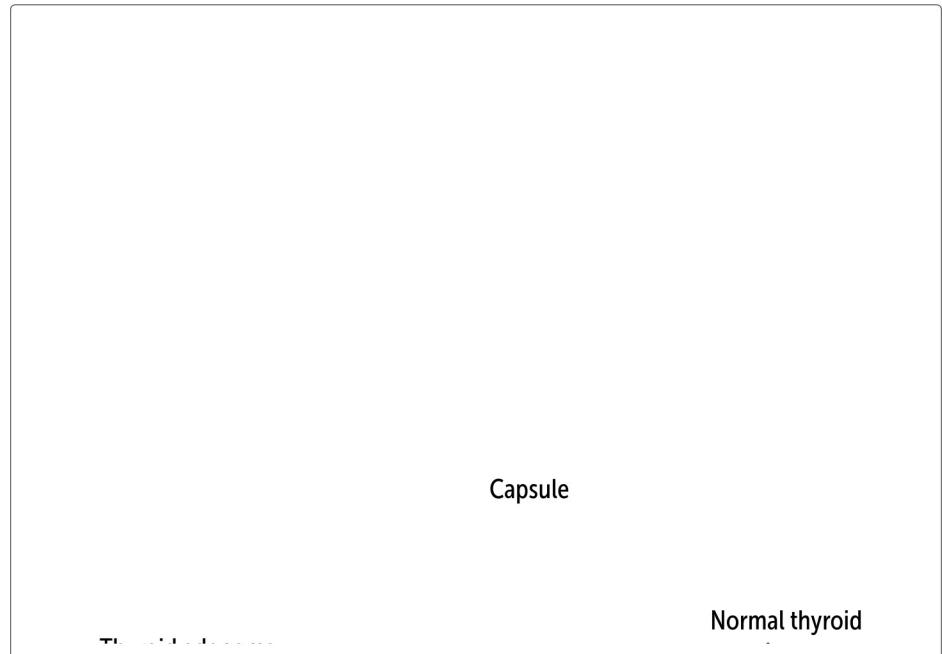
As noted, benign tumor names have two parts. The prefix refers to the cell or tissue of origin. The second part (suffix) is -oma. Many cell-of-origin prefixes will already be familiar to you: myo- refers to muscle cells; lipo- refers to fat cells, and osteo- refers to bone. Some may be new to you, but you'll catch on quickly! Here are some examples of prefixes:

- Adeno- refers to glandular cells.
- Leiomyo- refers to smooth muscle cells.
- Rhabdomyo- refers to skeletal muscle cells.
- Angio- refers to vessels of any type.
- Hemangio- refers to blood vessels.
- Lymphangio- refers to lymphatic vessels.

Here are some examples of benign tumor names:

- Benign tumor of glandular cells = adeno (glandular cells) + oma = adenoma
- Benign tumor of smooth muscle = leiomyo (smooth muscle) + oma = leiomyoma
- Benign tumor of bone = osteo (bone) + oma = osteoma

Figure 1 shows an adenoma of the thyroid gland. The adenoma is surrounded by a capsule, as is often the case in benign tumors. A small amount of normal thyroid tissue is present to the right.



Capsule

Normal thyroid

## QUIZ

Tap image for quiz

Figure 1

There are a couple of exceptions: papilloma and nevus. Papillomas are benign tumors of epithelial tissue that have tiny finger-like bumps (projections) at their surfaces. This finger-like growth pattern is called a papillary pattern. In Latin, papilla means a small elevation or swelling in the skin, like a nipple, so the name does have some logic to it!

A nevus (commonly called a mole) is a benign tumor of melanocytes.

Technically, a benign tumor of melanocytes should be called a melanoma, but for unknown reasons, the term melanoma is used for the malignant version of this tumor. So we're stuck with nevus.

What is the name for a benign tumor of blood vessels?

## Malignant Tumors

Remember that the body is made up of two major classes of tissue: epithelial tissues and mesenchymal tissues. Epithelium consists of densely packed cells atop a basement membrane; this tissue covers various surfaces and lines cavities within the body.

Mesenchymal tissues are “soft” tissues, or connective tissues, that make up the bulk of the body (eg, muscle, bone, cartilage, fat, and connective tissue). These tissues are derived from mesenchyme, a gelatinous substance present during early embryogenesis. Mesenchyme arises from mesoderm, the germ cell layer sandwiched between the ectoderm and the endoderm.

endoderm.

When a malignant tumor is derived from epithelial tissue, “carcinoma” is added. For example:

- Malignant tumor of glandular cells = adeno (glandular cells) + carcinoma (glandular cells are epithelial) = adenocarcinoma
- Malignant tumor of squamous cells = squamous cell + carcinoma (squamous cells are epithelial) = squamous cell carcinoma

When a malignant tumor is derived from mesenchymal tissue, “sarcoma” is added. In Greek, sark or sark means flesh, so you can think of sarcomas as malignant tumors of fleshy tissues. For example: malignant tumor of smooth muscle = leiomyo (smooth muscle) + sarcoma (smooth muscle is mesenchymal) = leiomyosarcoma.

What is the name for a malignant tumor of fat cells?

## Exceptions to the Rule

Some malignant tumor names don't follow the rules. Some of these names sound like benign tumors, but they most definitely are malignant:

- Glioblastoma: malignant tumor of astrocytes in the brain and spinal cord
- Lymphoma: malignant tumor of lymphocytes
- Leukemia: malignant tumor of white blood cells
- Mesothelioma: malignant tumor of mesothelial cells
- Melanoma: malignant tumor of melanocytes
- Myeloma: malignant tumor of plasma cells
- Seminoma: malignant tumor of male germ cells

## Names That Sound Like Tumors But Aren't

The names of some lesions include the -oma suffix, but these lesions are not actually neoplasms. Hamartomas are non-neoplastic regions of disorganized tissue that are indigenous to the site at which they are found. For example, a pulmonary hamartoma is a localized area of disorganized tissue within the lung.

Hamartomas are usually harmless but can sometimes cause bothersome or harmful effects. And the terminology is often inconsistent: many lesions that some consider hamartomas are considered by others to be neoplastic.

### CLINICAL CORRELATION

A characteristic of the autosomal dominant disease tuberous sclerosis is hamartomas of the skin and central nervous system.

Another example of a name that ends in -oma but is not a neoplasm is the term choristoma, which refers to the growth of microscopically normal cells in an abnormal location. For example, a small nodule of normal-appearing thyroid tissue located in the thymus would be considered a choristoma.

## What is a hamartoma?

### CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to SN, how do you speak to him about the significance of an adenoma?

You type a message back to SN: "Not to worry. The word adenoma means a benign, noncancerous growth of the normal glandular tissue of the colon. No cancer was found. That's good news. We will need to repeat the colonoscopy, and we can talk about when the best timing would be at your next visit."

Please let me know if you have any further questions." SN thanks you for your prompt reply. In his follow-up visit, you jointly decide to repeat the colonoscopy in 5 years.

## Summary

- Neoplasia is the unregulated, monoclonal proliferation of cells; a neoplasm can be benign or malignant.
- Benign tumors remain localized and do not metastasize, while malignant tumors are capable of metastasizing; "cancer" refers to malignant tumors.
- In general, tumor names have two parts: the first part refers to the tumor's tissue of origin, and the second part includes the suffix -oma.
- Benign tumors are named by adding -oma to the tumor's tissue of origin (eg, adenoma).
- Malignant tumors are named by adding "carcinoma" (if the tumor is derived from epithelial cells) or "sarcoma" (if the tumor is derived from mesenchymal cells) to the tumor's tissue of origin (eg, adenocarcinoma).
- There are many exceptions to the general rules for tumor nomenclature; it's important to become familiar with the most common ones to avoid confusion.

## Review Questions

1. A patient receives a diagnosis of squamous cell carcinoma of the lung. According to the standard rules of tumor nomenclature, which of the

following is true about this lesion?

- A. It can also be called a papilloma
- B. It can invade locally and spread to distant anatomic sites
- C. It is a benign tumor
- D. It is not cancer
- E. The tissue of origin is mesenchymal

Explanation (requires correct answer)

2. A man is told he has a fibroma. According to the standard rules of tumor nomenclature, which of the following is true about this lesion?

- A. It is a benign tumor
- B. It is cancer
- C. It is derived from muscle cells
- D. It has the potential to metastasize
- E. It will contain many areas of necrosis

Explanation (requires correct answer)

# Cancer Staging and Grading

Last updated September 25, 2024  17 min read 

**Author:** ScholarRx

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## Learning Objectives (4)

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

- 1 Explain what tumor markers are, and describe how they are used to determine prognosis.
- 2 Define grading, and explain some histologic features used in grading tumors.
- 3 Define staging, and explain the TNM system of staging tumors.
- 4 Define prognosis, and explain in general how prognosis is determined for patients with cancer.

disease. Establishing a prognosis is essential for both patients and doctors because it helps each determine the next step of action. Treatments, or lack thereof, depend on the expected course of the disease. If a patient has a terminal prognosis (ie, no chance of surviving the disease) and is only expected to live for a limited amount of time, that knowledge will help them decide how to best spend the remaining time and make plans accordingly.

## Why Are There So Many Different Prognostic Parameters?

Different outcome measures are used to determine a prognosis. This can sometimes be very confusing to both patients and students. Survival, for example, can be measured with specific qualifications. Survival rate might be measured at differing end points, such as 5 years or 10 years. Or it might be qualified as cancer-specific, disease-free, or overall:

- **Cancer-specific survival** is the percentage of patients with a specific type and stage of cancer who have not died from that cancer within a certain period of time after their diagnosis. This does not mean that all patients in this group are cancer-free, just that their disease has not resulted in their death from the time of diagnosis until a specified end point.
- **Disease-free survival** is the percentage of patients who have no signs of cancer during a certain period of time after completing their treatment.
- **Overall survival** refers to the percentage of patients with a specific type and stage of cancer who have not died from any cause in a certain period of time after their cancer diagnosis.

Each of these measures is clearly different from the other and each a

different way of describing one's prognosis.

## What Determines Prognosis?

Many factors are involved in determining a patient's prognosis. The type of cancer is, of course, very important. Some cancers carry a much grimmer prognosis than others. For example, the 5-year overall survival rate for all patients with prostate cancer is 98%; for Hodgkin lymphoma, it is 86%; for colorectal cancer, the rate is 65%; and for lung cancer, the 5-year overall survival rate is only 18%.

INSTRUCTOR NOTE

There is no need to memorize these percentages at this point - when we get to the specific systems, we will discuss this further

MARIA PLUMMER

However, the type of cancer a patient has is only one part of the story. Notice how the term "overall survival" is used above. This means that the stated survival rates are averages for *all* patients with these types of cancer. But within each type of cancer, there is a range of survival, and that range is often huge—with some patients surviving into old age and others surviving less than a few weeks. So once we know what type of cancer a patient has, what factors do we use to establish that particular patient's prognosis?

**Stage of the Cancer.** Stage defines how large the cancer is and how far it has spread. We will cover this in more detail below. Consider, though, that patients with stage 1 small cell lung cancer have a 5-year survival rate of 31%, while patients with stage 4 disease have only a 2% 5-year survival rate. Staging is generally the most important factor for determining prognosis.

**Grade of Cancer.** Grade refers to the histologic characteristics of the cancer. We will cover this in more detail later. Suffice it to say that, like stage, the higher the grade of a cancer, the worse its prognosis.

**Genetic and Molecular Characteristics.** Cancers can have specific molecular characteristics, such as particular gene mutations or cell surface receptors. Specific molecular features can confer a better or worse prognosis. Some molecular characteristics of cancer can make it a target for a specific treatment, which can in turn affect prognosis. Examples include the *BRCA1* and *BRCA2* mutations in breast cancer as well as progesterone receptors, estrogen receptors, and HER2/Neu receptors in breast cancer. Breast cancers that are estrogen-receptor positive carry a better prognosis than those that do not, while cancers that are HER2/Neu negative carry a better prognosis than those that are positive.

**Tumor Markers.** These are measurable substances that help determine the severity of a cancer and a patient's response to treatment. Examples include prostate-specific antigen (PSA) for prostate cancer and carcinoembryonic antigen for gastrointestinal tumors.

**Age.** A patient's age and general health are also factors. Elderly patients and immunosuppressed patients (such as those with HIV or diabetes) tend to have a worse prognosis.

**Initial Response to Treatment.** If a patient responds very well to initial

treatment, it might improve their prognosis, while if a patient's cancer doesn't respond to treatment at all, the prognosis is usually worse.

**Severity of Certain Signs and Symptoms of Cancer.** These are often specific to individual cancers. One example is that patients who become hypercalcemic because of their cancer usually carry a worse prognosis (whether that's because of a paraneoplastic syndrome or because of bone metastasis). The same is true for patients who have cachexia (weakness, anorexia, muscle wasting, and fatigue caused by an illness).

What is generally the most important factor in determining a cancer patient's prognosis?

## What Are “Remission” and “Cure?”

In the context of cancer, cure means that there is no trace of cancer whatsoever and the cancer will never come back. When dealing with cancer, it is almost impossible for doctors to be able to make such a statement. We can't be sure that a few undetectable cancer cells no longer

remain.

This is why we so often hear the word “remission” when talking about cancer. **Remission** means that the signs and symptoms of cancer are either reduced or absent. **Partial remission** means that the cancer has responded to treatment and the signs and symptoms are alleviated, but they have not been completely eliminated.

**Complete remission** means all evidence, signs, and symptoms of cancer have disappeared. Even with complete remission, some undetected cancer cells may remain, and they might cause the cancer to grow back. This is why the word “cure” is seldom used when referring to the treatment of cancer, and it is also why patients with cancer must still be monitored for years after they are declared “cancer free.”

## What Is Cancer Staging?

The stage of a cancer is a measure of its size and how far it has spread. It is generally the most important prognostic factor for determining survival. The stage of a cancer has a scale of 0 through 4, and stage is usually determined using the **TNM system**. TNM stands for tumor, node, and metastasis.

Tumor refers to the size of the original tumor. It is quantified from 1-4, with 1 being the smallest and 4 being the largest.

STRUCTOR NOTE

Sometimes T refers to the extent of local invasion. For Example in a colon adenocarcinoma the T goes from 1 to 4 as the cancer

involves the different layers of the wall of the GI tract

MARIA PLUMMER

Node describes whether the cancer has invaded nearby lymph nodes. It is quantified from 0-3, with 0 meaning there has been no spread to lymph nodes and 3 referring to spread to many lymph nodes. After metastasis, this is the second most important of these three prognostic factors.

Metastasis describes a cancer’s spread to other organs in the body. It is the most important of these three prognostic factors. It is quantified with either 0 or 1, with 0 referring to no metastasis and 1 referring to metastasis.

The exact anatomical and molecular parameters that determine the specific stage of a cancer can be complex, and they greatly differ from one cancer to the other. A committee of experts establishes the exact criteria for each cancer.

Often, cancer stages will also be written with a number and a letter, such as stage 2A or stage 3B instead of stage 2 or stage 3. The letters are simply a system for further stratifying within stages. Stage 3A cancer carries a worse prognosis than a stage 2B cancer of the same type. For some cancers, there is even stratification within each of the TNM categories, such as T1a and T1b, etc. Describing these is beyond the scope of our lesson.

To illustrate how staging affects prognosis, [Table 1](#) lists the 5-year survival rate as a function of the stage of non–small cell lung cancer.

**Table 1**

Stage	Five-Year Survival Rate
1A	49%
1B	45%
2A	30%
2B	31%
3A	14%
3B	5%
4, or metastatic	1%

You can see how the stage of cancer can make a significant difference in a patient's prognosis.

INSTRUCTOR NOTE

Again, it is not important to memorize these percentages at this time

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## What Is Cancer Grading?

The grade of a tumor describes its histologic appearance and the number of mitoses visible in the cells. Cancers can range from well-differentiated, which is low grade, to undifferentiated or anaplastic, which is high grade.

which is low grade, to undifferentiated or anaplastic, which is high grade.

Well-differentiated cells bear a close resemblance to the cells of normal tissue, while anaplastic cells exhibit a complete lack of differentiation and do not resemble normal tissue cells at all. Poorly differentiated tumors are usually more aggressive than well-differentiated ones. Although grading is an important prognostic factor, it is not as important as staging.

What is the difference between the stage and grade of a cancer?

A good example of grading is how it is used to describe infiltrating ductal carcinoma, the most common type of invasive breast cancer. Grade 1 tumors are well-differentiated. They have cells that form glands within the breast stroma, and their nuclei are uniform with virtually no evidence of mitotic activity. On the other end of the spectrum, grade 3, poorly differentiated tumors have nests of neoplastic cells with no evidence of gland formation, along with marked nuclear atypia and substantial mitotic activity. Grade 2 is best thought of as the middle ground between these two extremes.

## What Are Tumor Markers?

INSTRUCTOR NOTE

Discussed in Intro to Neoplasia, part 2

MARIA PLUMMER

A tumor marker is a compound that can be measured in the serum or urine that is elevated in the presence of cancer. These markers are usually substances that are produced by the tumors, resulting in levels higher than is otherwise normal. Common examples include:

- CA19-9, a marker for pancreatic cancer
- Alpha-fetoprotein (AFP), a marker for hepatocellular carcinoma (HCC)
- Chromogranin, a marker for neuroendocrine tumors
- Prostate-specific antigen (PSA), a marker for prostate cancer
- CA-125, a marker for ovarian cancer

### CLINICAL CORRELATION

Prostate cancer is the most common cancer in men, and breast cancer is the most common cancer in women. Lung cancer is the second most common cancer in both men and women, and it is the most common cancer killer in both men and women as well. A better way to state this is to say that lung cancer has the greatest mortality across both men and women, while breast

cancer has the greatest morbidity for women and prostate cancer has the greatest morbidity for men.

Tumor markers should not be used as a primary tool for diagnosing or screening for cancer. Levels can vary from patient to patient and can be affected by specific patient characteristics, so they are not a reliable tool for diagnosis. (For example, PSA levels change as men age, so the threshold for elevated PSA levels is different for men of different ages. Therefore, PSA has low sensitivity and specificity for detecting prostate cancer.)

However, after a cancer diagnosis is established, tumor markers can be very useful. A physician can measure the baseline levels of a tumor marker and track the changes over time. A decrease usually signifies a positive response to treatment, while an increase suggests minimal response; this can influence prognosis. Markers can also be used to monitor patients after treatment. Once a patient's baseline level is established after treatment, an increasing tumor marker level later might suggest cancer recurrence.

Remember that PSA stands for **Prostate-Specific Antigen** to recall it is the tumor marker for prostate cancer.

## CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to PF, how do you explain the summary to him? What is his prognosis?

You explain to PF that the abbreviation is a way of reporting the staging of his lung cancer. Staging describes the size of the tumor (T), whether or not it has spread to the lymph nodes (N), and whether there is distant spread of the cancer or metastases (M). You explain that his tumor is between 4 and 5 cm in size, and there is no spread to either the lymph nodes or distant sites.

"With this information, we can give you some numbers about your prognosis. Your 5-year survival is 31%," you tell him.

## Summary

- Prognosis is a forecast of the likely course and outcome of a patient's disease. Having a prognosis helps inform patients and providers on the best steps in management.
- Numerous outcome measures are used when giving a prognosis. Because each type of cancer has a range of possible prognoses, each patient must be individually evaluated to determine an accurate prognosis.
- There are many factors involved in determining the prognosis for a patient with a particular type of cancer (eg, lung or breast cancer). In

general, the most important of these is the stage of the cancer (eg, stage 2 or stage 4).

- Cancer staging describes the size and spread of a tumor. We use the TNM system to establish the stage of a cancer. M refers to the distant metastasis of cancer, and it is the most important prognostic factor; lymph node involvement (N) is the second most important.
- The higher the cancer stage, the worse the prognosis.
- The grade of a cancer describes its histologic features.
- Grading also contributes to prognosis, with a high grade conferring a worse prognosis. However, grading is not as important a factor as staging.
- Tumor markers are measurable compounds that are useful for measuring response to cancer treatment, prognosis, or the recurrence of disease. They are generally not useful for diagnosis.

## Review Questions

### 1. Which of the following patients carries the worst prognosis?

- A. A 25-year-old man with stage 3 Hodgkin lymphoma
- B. A 50-year-old man with stage 2 colon cancer
- C. A 65-year-old woman with stage 3 estrogen receptor-positive breast cancer
- D. A 70-year-old man with stage 4 lung cancer
- E. A 75-year-old woman with stage 3 lung cancer

# Epidemiology of Cancer

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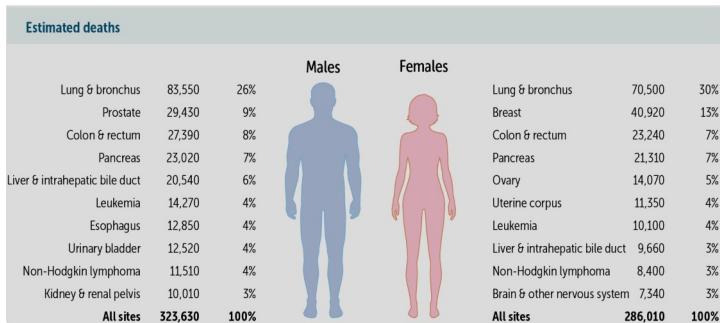
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## Learning Objectives (3)

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

- 1 Explain how and why cancer incidence has changed over the past several decades.
- 2 Describe environmental agents that affect cancer.
- 3 Explain how heredity affects cancer incidence.



**Figure 1**

There are many different types of cancer, and each has its own prognosis. Some types of cancer, like thyroid cancer, are almost always curable. Others, like pancreatic cancer, are almost always rapidly fatal. This is why the lists of the most common cancers and the cancers causing the most deaths look different!

For example, take a look at the most common cancers in men (prostate) and women (breast) in Figure 1. Although these cancers can be fatal, their overall prognosis is relatively good compared with lung cancer, which has a terrible prognosis. That's why so many more women die of lung cancer than breast cancer, even though the incidence of breast cancer is more than double the incidence of lung cancer. Thyroid cancer is fairly common, especially in women—but its prognosis is so good that it doesn't even make it onto the list of cancers causing the most deaths in women. Pancreatic cancer is uncommon, yet it causes almost as many deaths as does colon cancer.

What type of cancer causes the most deaths in both men and women in the United States?

## How Have Cervical, Colorectal, and Breast Cancers Changed in Incidence?

Let's take a detailed look at three cancers—cervical, colorectal, and breast—which incidences have changed in the past century. A common theme you will see is the development of screening tools for these cancers and how their use has affected the statistics.

### STRUCTOR NOTE

Please note, you do not need to know the specifics of these cancers at this time. Rather, these are being used as examples to incorporate the concepts. You will learn about these cancers in their respective systems. However, it is important to realize that many environment factors may cause cancers including infectious agents like HPV which may lead to squamous cell carcinoma of the cervix (see further below).

CERVIX (SEE FURTHER BELOW)

MARIA PLUMMER

## Cervical Cancer

Cervical cancer arises in the epithelium of the cervix (the lowermost portion of the uterus, located in the superior portion of the vagina). Cervical cancer is caused by certain strains of human papillomavirus (HPV), a sexually transmitted infection. In the 1940s, cervical cancer was still a major cause of death in reproductive-aged women. Since then, two screening tools have been developed: the Pap smear and human papillomavirus (HPV) testing.

The Papanicolaou test (**Pap smear**) was introduced in the 1950s as a screening tool for cervical cancer. A Pap smear is done by collecting cells from the surface of the cervix with a swab and examining them under the microscope. By identifying abnormalities in the cervical cells, we are able to detect precancerous cervical lesions, which allows us to intervene early, before cervical cancer even develops.

The results have been dramatic. From 1955 to 1992 in the United States, both incidence and mortality from cervical cancer have decreased more than 60%! According to the most recent National Institutes of Health data, only about 7 in 100,000 US women developed cervical cancer in 2014; that's roughly 0.007% of the US female population. Worldwide, however, cervical cancer is still a scourge. In fact, 80% of cervical cancer occurs in developing countries. This is an area of global health that can be definitively addressed by increasing access to Pap smears in these countries.

**HPV testing by PCR** (polymerase chain reaction) is a more recently developed screening test for cervical cancer. Cervical cells are obtained in the same way as for a Pap smear and then are tested for high-risk strains of HPV. If high-risk HPV strains are present, the cervix is evaluated further for the presence of precancerous lesions. HPV PCR is being used more and may replace Pap smears in the future, at least in countries with access to this technology.

## Colorectal Cancer

Colorectal cancer arises in the colon and rectum. It mostly occurs in people older than 50 years, although it can occur in younger people as well. The incidence of colorectal cancer has actually increased worldwide since the 1900s in parallel with economic development and longer life expectancy. This trend of increasing rates has been especially true in developing countries such as urban China, where Western lifestyles and diets have been adopted.

As of 2010, 5%-6% of individuals worldwide are expected to develop colorectal cancer in their lifetimes. From 2003 to 2012, however, the incidence of colorectal cancer in the United States has decreased significantly—by 2%-4% in all major ethnic groups and in both men and women. This may be due to increased awareness of colorectal cancer screening, aided by campaigns such as Screen for Life, a national project of the Centers for Disease Control and Prevention (CDC) in the United States. There are two tests to be familiar with: the fecal occult blood test and colonoscopy.

The presence of blood in the stool in any adult is suspicious for occult bleeding from a tumor in the lower gastrointestinal tract. This is the basis

for the **fecal occult blood test**, a simple, cheap method of detecting blood in the stool. However, because blood in the stool is typically only present in more advanced colon cancers (and not in precancerous lesions such as colon polyps), the utility of this test in detecting early cancer is limited.

The gold-standard screening test for colon cancer is **colonoscopy**, in which a scope is used to visualize the colon and remove any polyps or other suspicious lesions before they have a chance to turn into colon cancer. Screening beginning at age 45 years is recommended for healthy individuals without a family history of cancer or personal history of cancer syndromes. However, nearly 33% of this healthy population has not been screened as recommended!

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What is the general trend (increasing or decreasing) of colorectal cancer in developing countries?

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## Breast Cancer

Breast cancer arises in the ducts and lobules of the breast. It is more

prevalent in women than men, and the current lifetime risk of breast cancer in a woman is 1 in 8, making it the most frequently diagnosed cancer in women. The incidence of breast cancer increased rapidly in the latter part of the 20th century. There are a few reasons to explain this: screening and changes in risk factors.

**Mammography**, an X-ray of breast tissue to screen for breast cancer, first started being used widely around the 1970s-1980s. Mammograms have actually increased the apparent incidence of breast cancer simply because it allows us to detect it much sooner.

Another reason for the increase in breast cancer in the late 20th century has to do with breast cancer risk factors. The greater a woman's exposure to **estrogen**, the more likely she is to develop breast cancer. In the 1960s, women began having fewer children and also began delaying childbearing until later in life. Both of these practices increase a woman's exposure to estrogen—and as a result, we saw an increase in breast cancer beginning in the 1980s.

**Obesity** also increases a woman's risk of developing breast cancer through complex mechanisms related to estrogen—so increasing rates of obesity also contributed to an increase in breast cancer incidence. Although obesity rates are still on the rise, childbearing trends have stabilized for the most part. And in recent years, the incidence of breast cancer has more or less stabilized as well.

## What Are the Environmental Risk Factors for Cancer?

The list of things that increase the risk of cancer is a long one, but it can be divided into two big categories: environmental factors and genetic factors.

We'll talk about genetic factors in the next section; here, we'll talk about the most important and well-characterized environmental factors.

Keep in mind that in the context of cancer risk factors, the term environmental is used to refer to any factor that doesn't fall into the genetic category. This means that there's a really wide range of environmental factors—everything from toxic exposure to childbearing patterns to dietary choices. Fortunately, many environmental factors, such as smoking, are avoidable!

It appears that for most cancers, environmental factors play a much bigger role than genetic factors. [Figure 2](#) shows the estimated number of cancer deaths caused by identifiable factors; note how small the family history slice is! Much of our understanding in this area comes from epidemiologic studies showing that specific cancers are much more common in some parts of the world than in others. For example, breast cancer is much more common in the United States than in Japan. Further, when people emigrate from Japan to the United States, their risk for developing breast cancer increases—and in subsequent generations, the risk approaches that of native-born US citizens.

**Figure 2**

Before we jump into our discussion of specific environmental factors, though, let's define a term that we'll be using frequently: carcinogen. Broadly defined, a carcinogen is simply something that can cause cancer. By this definition, the list of carcinogens is huge. It encompasses not only clearly harmful chemicals (like toxins) but also things like infectious agents, common food items, and even UV light. Sometimes, though, the term carcinogen is used more narrowly to refer to just those substances (like the constituents of cigarette smoke, for example) that have a well-understood, DNA-damaging mechanism. We'll adopt the broader definition in our discussion below.

## **Smoking**

Smoking, particularly cigarette smoking, causes more premature deaths in the United States than any other environmental factor. WOW! A little pause might be necessary here, just to let the enormity of that sentence sink in. Many of those premature deaths are due to diseases such as [myocardial infarction](#) and [stroke](#), both significantly more common in smokers. But smoking is a major risk factor for many different types of cancer, too—lung cancer, of course, but also cancers of the mouth, [esophagus](#), [pancreas](#), and [bladder](#), many of which have a high mortality rate.

## Diet

The list of dietary factors that may increase cancer risk is long, and it seems to be constantly growing and changing. Some of these factors, however, have been well-studied and are widely accepted as definite risk factors. For example, excessive amounts of refined carbohydrates and fat are both clearly associated with an increased risk of colorectal cancer.

Some dietary risk factors are known to be associated with particular carcinogens. For example, a high fat intake stimulates the liver to make more cholesterol and bile acids, both of which can be converted into carcinogens by the bacteria in the intestine. However, for many dietary factors, an underlying cancer-causing mechanism is not yet known.

## Alcohol Consumption

Excessive alcohol consumption increases risk for cancers of the mouth, larynx, and esophagus (and if the patient is also a smoker, the risk of these cancers is synergistically increased). Many patients with long-standing alcohol abuse develop alcoholic cirrhosis of the liver, a condition that predisposes the patient to developing hepatocellular carcinoma, or cancer of liver cells. Alcohol also increases the level of estrogen in the body, which increases the risk of breast cancer.

## Obesity

Obesity is increasing at an alarming rate not only in the United States, but also in other parts of the world. In women, obesity leads to excessive estrogen exposure, which increases the risk of breast and endometrial cancer. But obesity also contributes to cancer deaths in men. The increase in cancer risk is not trivial. In fact, the rates of cancer death in patients

with morbid obesity are more than 50% higher than they are in the rest of the population.

## Reproductive History

As mentioned previously, excessive estrogen exposure increases the risk of several types of cancer in women, including breast and endometrium. During pregnancy, higher levels of progesterone counterbalance estrogen, giving a little reprieve from estrogen stimulation. The fewer pregnancies a woman has, and the later in life they occur, the more estrogen she is exposed to overall.

## Radiation Exposure

Whether from therapeutic interventional procedures (such as radiation treatments for cancer) or from the sun's UV rays, radiation significantly increases the risk of cancer. Both types of radiation may damage the cell's DNA, leading to genetic mutations that can pave the way for the development of cancer.

## Infectious Agents

Infectious agents cause approximately 15% of all cancers worldwide, with a much higher incidence in developing countries. Several viruses are known to cause cancers (for example, HPV causes cervical cancer, and hepatitis viruses may cause hepatocellular carcinoma). Bacterial agents are less commonly implicated than viral agents, but one well-researched example is the bacterium *Helicobacter pylori*, which is causally related to both gastric carcinoma and a particular type of lymphoma called mucosa-associated lymphoid tissue (MALT) lymphoma.

## Occupational Agents

Several carcinogens are encountered primarily in occupational settings. A wide range of fields, from agriculture to construction to manufacturing, use specific agents that are known to cause cancer:

- Asbestos (in construction materials) is linked to several cancers, including mesothelioma.
- Benzene (in printing, paint, and light oil) is linked to acute myeloid leukemia.
- Radon (in underground mines and also in residential properties) is linked to lung cancer.
- Vinyl chloride (in refrigerants and adhesives) is linked to hepatic angiosarcoma.

As we can see, carcinogens are both diverse and widespread, and a solid awareness of them is critical to successfully preventing many cancers.

What type of cancer is linked to benzene exposure?

## What Are the Genetic Risk Factors for Cancer?

Because cancer arises from mutations in DNA, it is not surprising that heredity plays a role in cancer. This brings up the distinction of cancers that are inherited vs sporadic, ie, arising de novo. Sporadic cancers can be further classified as spontaneous cancers, which arise without carcinogen exposure, and induced cancers, which are the result of carcinogen exposure. Figure 3 illustrates this breakdown with several examples.

Figure 3

Hereditary cancers are caused by gene mutations that are passed on from the parent to child. Well known among these are mutations in the *BRCA* gene (hereditary breast and ovarian cancer syndrome) and in mismatch repair genes (Lynch syndrome). Lynch syndrome carries an increased risk of endometrial cancer and colorectal cancer.

Sporadic cancers do not come from inherited genetic mutations. Instead, at some point in the individual's life, he or she acquires a mutation in a somatic cell, which then leads to cancer. Because the somatic cell line is not passed onto the next generation, the individual's cancer is considered sporadic. Lung and bladder cancers are examples of sporadic cancers due to carcinogen exposure.

Hereditary cancers tend to manifest earlier and act more aggressively than their sporadic counterparts. For example, colon cancer can be either sporadic or hereditary. Sporadic cases usually appear after age 50 years and if detected early typically have a relatively good prognosis. In contrast, hereditary forms of colon cancer, such as those that develop in patients with Lynch syndrome, can occur as early as age 20 years and typically have a poor prognosis.

**Retinoblastoma**, the most common intraocular malignancy in children, is another cancer that has both hereditary and sporadic forms. This rapidly progressive cancer of the eye usually appears in childhood and is caused by inactivating mutations in the *RB* (retinoblastoma) gene. The *RB* gene is a tumor-suppressor gene, which means that in normal cells it encodes a product that puts the brakes on cell division. If just one of the two *RB* alleles is mutated, retinoblastoma does not develop because the remaining normal *RB* allele is able to compensate adequately. However, if both *RB* alleles are mutated in such a way that they don't work, then it's like having

the brakes go out in your car: there's nothing to stop the cell from dividing and proliferating, and as a result, retinoblastoma develops.

About 40% of cases of retinoblastoma are **hereditary** in nature. Patients with hereditary retinoblastoma inherit one normal *RB* allele and one mutated, inactive *RB* allele. The mutated *RB* allele is inherited in an **autosomal dominant** fashion. But because one mutated *RB* allele is not enough to cause retinoblastoma, the patient is said to be a carrier of the retinoblastoma trait. Without a second *RB* mutation, the patient will not develop retinoblastoma.

This doesn't sound so bad at first. How likely can it be that the patient would just spontaneously develop a mutation in the second *RB* allele? Unfortunately, very likely. In fact, carriers of the retinoblastoma trait are 10,000 times more likely to develop retinoblastoma as compared with noncarriers, often in both eyes. In addition, they have a very high risk of developing other aggressive malignancies, such as **osteosarcoma**.

The remaining 60% of cases of retinoblastoma are **spontaneous**, which means that the patient inherits two normal *RB* alleles and then at some point develops mutations in both alleles. The chances of this happening are pretty low. Patients who do develop spontaneous retinoblastoma do not have an increased risk of developing other cancers.

The explanation for these two patterns of retinoblastoma is known as the **"two-hit" hypothesis**. This hypothesis states that to develop retinoblastoma, two hits (mutations) are required: one in each *RB* allele. In hereditary cases, patients inherit one mutated *RB* allele, and the other allele undergoes mutation on its own. In spontaneous cases, the patient inherits two normal *RB* alleles, both of which undergo spontaneous mutation.

In hereditary retinoblastoma, what is the Mendelian mode of inheritance?

#### CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to FH, how do you respond to his comment?

You begin your discussion by explaining that factors other than family history contribute to a person's risk of cancer. In fact, you say that environmental factors and exposures actually play a bigger role than genetics. "Your tobacco and alcohol use are strong risk factors for cancer of the mouth, and I am concerned about the non-healing ulcer you have." FH agrees to a biopsy, and the results reveal squamous cell carcinoma.

## Summary

- Earlier detection of cancer has changed cancer mortality and prevalence.

- The most common cancers in men and women are prostate and breast cancer, respectively.
- The cancer that causes the most deaths in both men and women is lung cancer.
- Cervical cancer has decreased in prevalence in the United States largely due to the introduction of the Pap smear.
- Eighty percent of cervical cancers occur outside the United States in developing countries, where access to Pap smears is limited.
- Colorectal cancer is increasing in prevalence in developing countries but is decreasing in prevalence in the United States due to improved screening.
- Environmental factors, such as dietary choices and smoking, play a major role in the development of many types of cancer.
- Cancers may be sporadic or hereditary; hereditary cases appear at younger ages and act more aggressively than their sporadic counterparts.

## Review Questions

### 1. Which of the following is not a cancer screening tool?

- A. Colonoscopy
- B. Mammography
- C. Pap smear
- D. Urinalysis