

Epidemiology of Cancer

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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.

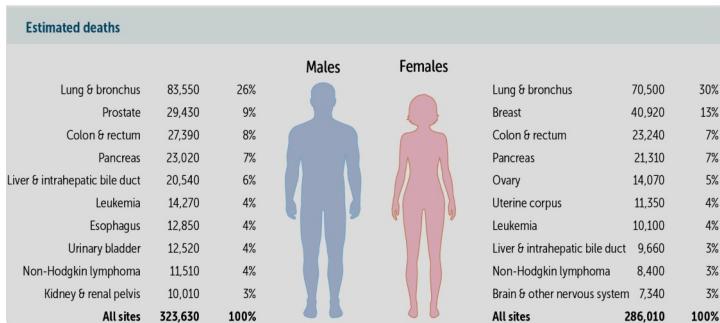


Figure 1

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.

INSTRUCTOR 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!

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

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