**The Development and Causes of Cancer**

The fundamental abnormality resulting in the development of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) is the continual unregulated proliferation of cancer cells. Rather than responding appropriately to the signals that control normal cell behavior, cancer cells grow and divide in an uncontrolled manner, invading normal tissues and organs and eventually spreading throughout the body. The generalized loss of growth control exhibited by cancer cells is the net result of accumulated abnormalities in multiple cell regulatory systems and is reflected in several aspects of cell behavior that distinguish cancer cells from their normal counterparts.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK9963/)

**Types of Cancer**

[Cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) can result from abnormal proliferation of any of the different kinds of cells in the body, so there are more than a hundred distinct types of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/), which can vary substantially in their behavior and response to treatment. The most important issue in cancer pathology is the distinction between benign and malignant tumors ([Figure 15.1](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2605/?report=objectonly)). A [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) is any abnormal proliferation of cells, which may be either benign or malignant. A [benign tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2937/), such as a common skin wart, remains confined to its original location, neither invading surrounding normal tissue nor spreading to distant body sites. A [malignant tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3165/), however, is capable of both invading surrounding normal tissue and spreading throughout the body via the circulatory or lymphatic systems ([metastasis](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3175/)). Only malignant tumors are properly referred to as cancers, and it is their ability to invade and metastasize that makes cancer so dangerous. Whereas benign tumors can usually be removed surgically, the spread of malignant tumors to distant body sites frequently makes them resistant to such localized treatment.

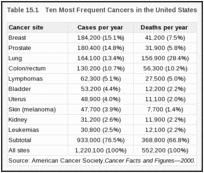
[Figure 15.1. A malignant tumor of the uterus.](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2605/?report=objectonly)

[**Figure 15.1**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2605/?report=objectonly)

A malignant tumor of the uterus. Micrographs of normal uterus (A) and a section of a uterine sarcoma (B). Note that the cancer cells (darkly stained) have invaded the surrounding normal tissue. (Cecil Fox/Molecular Histology, Inc.)

Both benign and malignant tumors are classified according to the type of cell from which they arise. Most cancers fall into one of three main groups: carcinomas, sarcomas, and leukemias or lymphomas. [Carcinomas](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2947/), which include approximately 90% of human cancers, are malignancies of [epithelial cells](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3045/). [Sarcomas](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3338/), which are rare in humans, are solid tumors of connective tissues, such as muscle, bone, cartilage, and fibrous tissue. [Leukemias](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3153/) and [lymphomas](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3160/), which account for approximately 8% of human malignancies, arise from the blood-forming cells and from cells of the immune system, respectively. Tumors are further classified according to tissue of origin (e.g., lung or breast carcinomas) and the type of cell involved. For example, fibrosarcomas arise from fibroblasts, and erythroid leukemias from precursors of [erythrocytes](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3047/) (red blood cells).

Although there are many kinds of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/), only a few occur frequently ([Table 15.1](https://www.ncbi.nlm.nih.gov/books/NBK9963/table/A2606/?report=objectonly)). More than a million cases of cancer are diagnosed annually in the United States, and more than 500,000 Americans die of cancer each year. Cancers of 10 different body sites account for more than 75% of this total cancer incidence. The four most common cancers, accounting for more than half of all cancer cases, are those of the breast, prostate, lung, and colon/rectum. Lung cancer, by far the most lethal, is responsible for nearly 30% of all cancer deaths.

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[**Table 15.1**](https://www.ncbi.nlm.nih.gov/books/NBK9963/table/A2606/?report=objectonly)

Ten Most Frequent Cancers in the United States.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK9963/)

**The Development of Cancer**

One of the fundamental features of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) is [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) clonality, the development of tumors from single cells that begin to proliferate abnormally. The single-cell origin of many tumors has been demonstrated by analysis of X chromosome inactivation ([Figure 15.2](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2608/?report=objectonly)). As discussed in Chapter 8, one member of the X chromosome pair is inactivated by being converted to [heterochromatin](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3112/) in female cells. X inactivation occurs randomly during embryonic development, so one X chromosome is inactivated in some cells, while the other X chromosome is inactivated in other cells. Thus, if a female is heterozygous for an X chromosome [gene](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3080/), different alleles will be expressed in different cells. Normal tissues are composed of mixtures of cells with different inactive X [chromosomes](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2977/), so expression of both alleles is detected in normal tissues of heterozygous females. In contrast, tumor tissues generally express only one [allele](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2901/) of a heterozygous X chromosome gene. The implication is that all of the cells constituting such a tumor were derived from a single cell of origin, in which the pattern of X inactivation was fixed before the tumor began to develop.

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[**Figure 15.2**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2608/?report=objectonly)

Tumor clonality. Normal tissue is a mosaic of cells in which different X chromosomes (X1 and X2) have been inactivated. Tumors develop from a single initially altered cell, so each tumor cell displays the same pattern of X inactivation (X1 inactive, X [(more...)](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2608/?report=objectonly)

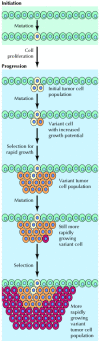
The clonal origin of tumors does not, however, imply that the original progenitor cell that gives rise to a [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) has initially acquired all of the characteristics of a [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cell. On the contrary, the development of cancer is a multistep process in which cells gradually become malignant through a progressive series of alterations. One indication of the multistep development of cancer is that most cancers develop late in life. The incidence of colon cancer, for example, increases more than tenfold between the ages of 30 and 50, and another tenfold between 50 and 70 ([Figure 15.3](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2609/?report=objectonly)). Such a dramatic increase of cancer incidence with age suggests that most cancers develop as a consequence of multiple abnormalities, which accumulate over periods of many years.

[Figure 15.3. Increased rate of colon cancer with age.](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2609/?report=objectonly)

[**Figure 15.3**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2609/?report=objectonly)

Increased rate of colon cancer with age. Annual death rates from colon cancer in the United States. (Data from J. Cairns, 1978. *Cancer: Science and Society*, New York: W. H. Freeman.)

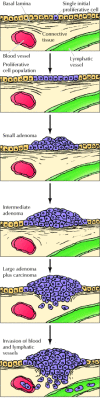
At the cellular level, the development of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) is viewed as a multistep process involving [mutation](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3191/) and selection for cells with progressively increasing capacity for proliferation, survival, invasion, and [metastasis](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3175/) ([Figure 15.4](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2610/?report=objectonly)). The first step in the process, [**tumor**](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/)**initiation**, is thought to be the result of a genetic alteration leading to abnormal proliferation of a single cell. Cell proliferation then leads to the outgrowth of a population of clonally derived tumor cells. **Tumor progression** continues as additional mutations occur within cells of the tumor population. Some of these mutations confer a selective advantage to the cell, such as more rapid growth, and the descendants of a cell bearing such a mutation will consequently become [dominant](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3022/) within the tumor population. The process is called clonal selection, since a new [clone](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2982/) of tumor cells has evolved on the basis of its increased growth rate or other properties (such as survival, invasion, or metastasis) that confer a selective advantage. Clonal selection continues throughout tumor development, so tumors continuously become more rapid-growing and increasingly malignant.

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[**Figure 15.4**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2610/?report=objectonly)

Stages of tumor development. The development of cancer initiates when a single mutated cell begins to proliferate abnormally. Additional mutations followed by selection for more rapidly growing cells within the population then result in progression of [(more...)](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2610/?report=objectonly)

Studies of colon carcinomas have provided a clear example of [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) progression during the development of a common human malignancy ([Figure 15.5](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2611/?report=objectonly)). The earliest stage in tumor development is increased proliferation of colon [epithelial cells](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3045/). One of the cells within this proliferative cell population is then thought to give rise to a small benign neoplasm (an [adenoma](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2897/) or [polyp](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3268/)). Further rounds of clonal selection lead to the growth of adenomas of increasing size and proliferative potential. Malignant carcinomas then arise from the benign adenomas, indicated by invasion of the tumor cells through the [basal lamina](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2933/) into underlying connective tissue. The [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells then continue to proliferate and spread through the connective tissues of the colon wall. Eventually the cancer cells penetrate the wall of the colon and invade other abdominal organs, such as the bladder or small intestine. In addition, the cancer cells invade blood and lymphatic vessels, allowing them to metastasize throughout the body.

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[**Figure 15.5**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2611/?report=objectonly)

Development of colon carcinomas. A single initially altered cell gives rise to a proliferative cell population, which progresses first to benign adenomas of increasing size and then to malignant carcinoma. The cancer cells invade the underlying connective [(more...)](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2611/?report=objectonly)

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**Causes of Cancer**

Substances that cause [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/), called [carcinogens](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2946/), have been identified both by studies in experimental animals and by epidemiological analysis of cancer frequencies in human populations (e.g., the high incidence of lung cancer among cigarette smokers). Since the development of malignancy is a complex multistep process, many factors may affect the likelihood that cancer will develop, and it is overly simplistic to speak of single causes of most cancers. Nonetheless, many agents, including radiation, chemicals, and viruses, have been found to induce cancer in both experimental animals and humans.

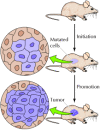
Radiation and many chemical carcinogens ([Figure 15.6](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2613/?report=objectonly)) act by damaging [DNA](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3010/) and inducing mutations. These carcinogens are generally referred to as initiating agents, since the induction of mutations in key target genes is thought to be the initial event leading to [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) development. Some of the initiating agents that contribute to human cancers include solar ultraviolet radiation (the major cause of skin cancer), carcinogenic chemicals in tobacco smoke, and aflatoxin (a potent liver [carcinogen](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2946/) produced by some molds that contaminate improperly stored supplies of peanuts and other grains). The carcinogens in tobacco smoke (including benzo(*a*)pyrene, dimethylnitrosamine, and nickel compounds) are the major identified causes of human cancer. Smoking is the undisputed cause of 80 to 90% of lung cancers, as well as being implicated in cancers of the oral cavity, pharynx, larynx, esophagus, and other sites. In total, it is estimated that smoking is responsible for nearly one-third of all cancer deaths—an impressive toll for a single carcinogenic agent.

[Figure 15.6. Structure of representative chemical carcinogens.](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2613/?report=objectonly)

[**Figure 15.6**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2613/?report=objectonly)

Structure of representative chemical carcinogens.

Other carcinogens contribute to [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) development by stimulating cell proliferation, rather than by inducing mutations. Such compounds are referred to as [tumor promoters](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3409/), since the increased cell division they induce is required for the outgrowth of a proliferative cell population during early stages of [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) development. The [phorbol esters](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3243/) that stimulate cell proliferation by activating [protein kinase C](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3292/) (see [Figure 13.26](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2234/figure/A2246/?report=objectonly)) are classic examples. Their activity was defined by studies of chemical induction of skin tumors in mice ([Figure 15.7](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2614/?report=objectonly)). Tumorigenesis in this system can be initiated by a single treatment with a mutagenic [carcinogen](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2946/). Tumors do not develop, however, unless the mice are subsequently treated with a [tumor promoter](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3409/) (usually a phorbol ester) to stimulate proliferation of the mutated cells.

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[**Figure 15.7**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2614/?report=objectonly)

Induction of tumors in mouse skin. Tumors are initiated by mutations induced by a carcinogen. Development of a tumor then requires treatment with a tumor promoter to stimulate proliferation of the mutated cells.

Hormones, particularly estrogens, are important as [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) promoters in the development of some human cancers. The proliferation of cells of the uterine endometrium, for example, is stimulated by [estrogen](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3048/), and exposure to excess estrogen significantly increases the likelihood that a woman will develop endometrial [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/). The risk of endometrial cancer is therefore substantially increased by long-term postmenopausal estrogen replacement therapy with high doses of estrogen alone. Fortunately, this risk is minimized by administration of [progesterone](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3279/) to counteract the stimulatory effect of estrogen on endometrial cell proliferation. However, long-term therapy with combinations of estrogen and progesterone may lead to an increased risk of breast cancer.

In addition to chemicals and radiation, some viruses induce [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) both in experimental animals and in humans. The common human cancers caused by viruses include liver cancer and cervical [carcinoma](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2947/), which together account for 10 to 20% of worldwide cancer incidence. These viruses are important not only as causes of human cancer; as discussed later in this chapter, studies of [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) viruses have played a key role in elucidating the molecular events responsible for the development of cancers induced by both viral and nonviral carcinogens.

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**Properties of Cancer Cells**

The uncontrolled growth of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells results from accumulated abnormalities affecting many of the cell regulatory mechanisms that have been discussed in preceding chapters. This relationship is reflected in several aspects of cell behavior that distinguish cancer cells from their normal counterparts. Cancer cells typically display abnormalities in the mechanisms that regulate normal cell proliferation, differentiation, and survival. Taken together, these characteristic properties of cancer cells provide a description of malignancy at the cellular level.

The uncontrolled proliferation of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells *in vivo* is mimicked by their behavior in cell culture. A primary distinction between cancer cells and normal cells in culture is that normal cells display **density-dependent inhibition**of cell proliferation ([Figure 15.8](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2616/?report=objectonly)). Normal cells proliferate until they reach a finite cell density, which is determined in part by the availability of [growth factors](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3104/) added to the culture medium (usually in the form of serum). They then cease proliferating and become quiescent, arrested in the [G0](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3076/) stage of the cell cycle (see [Figure 14.6](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2433/figure/A2441/?report=objectonly)). The proliferation of most cancer cells, however, is not sensitive to density-dependent inhibition. Rather than responding to the signals that cause normal cells to cease proliferation and enter G0, [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) cells generally continue growing to high cell densities in culture, mimicking their uncontrolled proliferation *in vivo*.

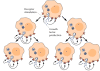
[Figure 15.8. Density-dependent inhibition.](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2616/?report=objectonly)

[**Figure 15.8**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2616/?report=objectonly)

Density-dependent inhibition. Normal cells proliferate in culture until they reach a finite cell density, at which point they become quiescent. Tumor cells, however, continue to proliferate independent of cell density.

A related difference between normal cells and [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells is that many cancer cells have reduced requirements for extracellular [growth factors](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3104/). As discussed in Chapter 13, the proliferation of most cells is controlled, at least in part, by [polypeptide](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3269/) growth factors. For some cell types, particularly fibroblasts, the availability of serum growth factors is the principal determinant of their proliferative capacity in culture. The growth factor requirements of these cells are closely related to the phenomenon of density-dependent inhibition, since the density at which normal fibroblasts become quiescent is proportional to the concentration of serum growth factors in the culture medium.

The growth factor requirements of many [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) cells are reduced compared to their normal counterparts, contributing to the unregulated proliferation of tumor cells both *in vitro* and *in vivo*. In some cases, [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells produce [growth factors](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3104/) that stimulate their own proliferation ([Figure 15.9](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2617/?report=objectonly)). Such abnormal production of a growth factor by a responsive cell leads to continuous autostimulation of cell division (**autocrine growth stimulation**), and the cancer cells are therefore less dependent on growth factors from other, physiologically normal sources. In other cases, the reduced growth factor dependence of cancer cells results from abnormalities in intracellular signaling systems, such as unregulated activity of growth factor receptors or other [proteins](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3297/) (e.g., [Ras](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3308/) proteins or protein kinases) that were discussed in Chapter 13 as elements of signal transduction pathways leading to cell proliferation.

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[**Figure 15.9**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2617/?report=objectonly)

Autocrine growth stimulation. A cell produces a growth factor to which it also responds, resulting in continuous stimulation of cell proliferation.

Cancer cells are also less stringently regulated than normal cells by cell-cell and cell-[matrix](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3167/) interactions. Most [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/)cells are less adhesive than normal cells, often as a result of reduced expression of cell surface adhesion molecules. For example, loss of E-cadherin, the principal adhesion molecule of [epithelial cells](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3045/), is important in the development of carcinomas (epithelial cancers). As a result of reduced expression of [cell adhesion molecules](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2957/), cancer cells are comparatively unrestrained by interactions with other cells and tissue components, contributing to the ability of malignant cells to invade and metastasize. The reduced adhesiveness of cancer cells also results in morphological and cytoskeletal alterations: Many [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) cells are rounder than normal, in part because they are less firmly attached to either the [extracellular matrix](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3056/) or neighboring cells.

A striking difference in the cell-cell interactions displayed by normal cells and those of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells is illustrated by the phenomenon of [contact inhibition](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2993/) ([Figure 15.10](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2618/?report=objectonly)). Normal fibroblasts migrate across the surface of a culture dish until they make contact with a neighboring cell. Further cell migration is then inhibited, and normal cells adhere to each other, forming an orderly array of cells on the culture dish surface. Tumor cells, in contrast, continue moving after contact with their neighbors, migrating over adjacent cells, and growing in disordered, multilayered patterns. Not only the movement but also the proliferation of many normal cells is inhibited by cell-cell contact, and cancer cells are characteristically insensitive to such [contact inhibition](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2993/) of growth.

[Figure 15.10. Contact inhibition.](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2618/?report=objectonly)

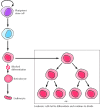
[**Figure 15.10**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2618/?report=objectonly)

Contact inhibition. Light micrographs (left) and scanning electron micrographs (right) of normal fibroblasts and tumor cells. The migration of normal fibroblasts is inhibited by cell contact, so they form an orderly side-by-side array on the surface of [(more...)](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2618/?report=objectonly)

Two additional properties of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells affect their interactions with other tissue components, thereby playing important roles in invasion and [metastasis](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3175/). First, malignant cells generally secrete proteases that digest [extracellular matrix](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3056/) components, allowing the cancer cells to invade adjacent normal tissues. Secretion of collagenase, for example, appears to be an important determinant of the ability of carcinomas to digest and penetrate through basal laminae to invade underlying connective tissue (see [Figure 15.5](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2611/?report=objectonly)). Second, cancer cells secrete [growth factors](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3104/) that promote the formation of new blood vessels ([angiogenesis](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2911/)). Angiogenesis is needed to support the growth of a [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/)beyond the size of about a million cells, at which point new blood vessels are required to supply oxygen and nutrients to the proliferating tumor cells. Such blood vessels are formed in response to growth factors, secreted by the tumor cells, that stimulate proliferation of endothelial cells in the walls of capillaries in surrounding tissue, resulting in the outgrowth of new capillaries into the tumor. The formation of such new blood vessels is important not only in supporting tumor growth, but also in metastasis. The actively growing new capillaries formed in response to angiogenic stimulation are easily penetrated by the tumor cells, providing a ready opportunity for cancer cells to enter the circulatory system and begin the metastatic process.

Another general characteristic of most [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells is that they fail to differentiate normally. Such defective differentiation is closely coupled to abnormal proliferation, since, as discussed in Chapter 14, most fully differentiated cells either cease cell division or divide only rarely. Rather than carrying out their normal differentiation program, cancer cells are usually blocked at an early stage of differentiation, consistent with their continued active proliferation.

The leukemias provide a particularly good example of the relationship between defective differentiation and malignancy. All of the different types of blood cells are derived from a common [stem cell](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3365/) in the bone marrow (see [Figure 14.44](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2499/figure/A2503/?report=objectonly)). Descendants of these cells then become committed to specific differentiation pathways. Some cells, for example, differentiate to form [erythrocytes](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3047/) whereas others differentiate to form lymphocytes, granulocytes, or macrophages. Cells of each of these types undergo several rounds of division as they differentiate, but once they become fully differentiated, cell division ceases. Leukemic cells, in contrast, fail to undergo terminal differentiation ([Figure 15.11](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2619/?report=objectonly)). Instead, they become arrested at early stages of maturation at which they retain their capacity for proliferation and continue to reproduce.

[](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2619/?report=objectonly)

[**Figure 15.11**](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2619/?report=objectonly)

Defective differentiation and leukemia. Different types of blood cells develop from a multipotential (pluripotent) stem cell in the bone marrow. The precursors of differentiated cells undergo several rounds of cell division as they mature, but cell division [(more...)](https://www.ncbi.nlm.nih.gov/books/NBK9963/figure/A2619/?report=objectonly)

As discussed in Chapter 13, [programmed cell death](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3280/), or [apoptosis](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2918/), is an integral part of the differentiation program of many cell types, including blood cells. Many [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells fail to undergo [apoptosis](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2918/), and therefore exhibit increased life spans compared to their normal counterparts. This failure of cancer cells to undergo [programmed cell death](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3280/)contributes substantially to [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) development. For example, the survival of many normal cells is dependent on signals from [growth factors](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3104/) or from the [extracellular matrix](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3056/) that prevent apoptosis. In contrast, tumor cells are often able to survive in the absence of growth factors required by their normal counterparts. Such a failure of tumor cells to undergo apoptosis when deprived of normal environmental signals may be important not only in primary tumor development but also in the survival and growth of metastatic cells in abnormal tissue sites. Normal cells also undergo apoptosis following [DNA](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3010/) damage, while many cancer cells fail to do so. In this case, the failure to undergo apoptosis contributes to the resistance of cancer cells to irradiation and many chemotherapeutic drugs, which act by damaging DNA. Abnormal cell survival, as well as cell proliferation, thus plays a major role in the unrelenting growth of cancer cells in an animal.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK9963/)

**Transformation of Cells in Culture**

The study of [tumor](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3407/) induction by radiation, chemicals, or viruses requires experimental systems in which the effects of a carcinogenic agent can be reproducibly observed and quantitated. Although the activity of carcinogens can be assayed in intact animals, such experiments are difficult to quantitate and control. The development of *in vitro* assays to detect the conversion of normal cells to tumor cells in culture, a process called **cell transformation**, therefore represented a major advance in [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) research. Such assays are designed to detect transformed cells, which display the *in vitro* growth properties of tumor cells, following exposure of a culture of normal cells to a carcinogenic agent. Their application has allowed experimental analysis of cell transformation to reach a level of sophistication that could not have been attained by studies in whole animals alone.

The first and most widely used assay of cell transformation is the focus assay, which was developed by Howard Temin and Harry Rubin in 1958. The focus assay is based on the ability to recognize a group of transformed cells as a morphologically distinct “focus” against a background of normal cells on the surface of a culture dish. The focus assay takes advantage of three properties of transformed cells: altered morphology, loss of [contact inhibition](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2993/), and loss of density-dependent inhibition of growth. The result is the formation of a colony of morphologically altered transformed cells that overgrow the background of normal cells in the culture. Such foci of transformed cells can usually be detected and quantified within a week or two after exposure to a carcinogenic agent. In general, cells transformed *in vitro* are able to form tumors following inoculation into susceptible animals, supporting *in vitro* transformation as a valid indicator of the formation of [cancer](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A2944/) cells.