

Part I

An Introduction to Cancer

Chapter 1

Cancer: Descriptive Overview

Cancer is a disease in which cells propagate uncontrollably. These cells can come from many different parts of the body and the reasons for the uncontrolled growth are manifold.

1.1

Patient level: incidence, classification, treatment, and mortality

At the whole-body level, we think of cancer in terms of its incidence, classification, treatment, and mortality. We want to know what types of cancer people get, how it is treated, and when it will be fatal.

Although we will not focus on it in this class, epidemiology, incidence rates, and the study of who gets cancer and why is very important.

Cancer is a disease of old age. We are living longer, so more people now get cancer and die of cancer.

.....
Most common cancers are skin, breast, prostate, colorectal, and lung

As illustrated in Figure 1.1, the most common cancers are skin, breast, prostate, colorectal, and lung.

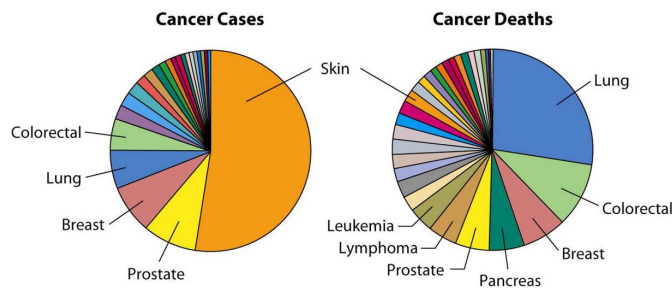


Figure 1.1: Frequencies of cancer cases and cancer death in the US in 2004.

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1.1. PATIENT LEVEL: INCIDENCE, CLASSIFICATION, TREATMENT, AND MORTALITY

Cancers are classified into four categories

Cancer can be subdivided into over a hundred different diseases based on a number of categories. Here, we classify cancers into four broad categories that are indicative of a few key characteristics.

... Carcinomas are tumors of the epithelial cell layers that line organs ... **carcinomas** induce 80% of cancer-related deaths in the Western world. **squamous cell** carcinomas refer to tumors originating in sheets of cells that line a cavity and protect cells underneath, for example cells lining the skin or esophagus. **adenocarcinomas** refer to tumors originating in sheets of secretory cells that line a glandular duct and secrete substances into the cavity they line. The most common carcinomas are shown in Figure 1.2.

Table 2.1 Carcinomas

(A) Tissue sites of more common types of adenocarcinoma	(B) Tissue sites of more common types of squamous cell carcinoma	(C) Other types of carcinoma
lung colon breast pancreas stomach esophagus prostate endometrium ovary	skin nasal cavity oropharynx larynx lung esophagus cervix	small-cell lung carcinoma large-cell lung carcinoma hepatocellular carcinoma renal cell carcinoma transitional-cell carcinoma (of urinary bladder)

Table 2-1 The Biology of Cancer (© Garland Science 2007)

Figure 1.2: The most common carcinomas.

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... Sarcomas are tumors forming in connective tissue cells ... **sarcomas** comprise only 1% of human clinical tumors. These tumors derive from **mesenchymal** cells such as bone, muscle, cartilage, and fat cells. The most common sarcomas are shown in Figure 1.3.

Table 2.2 Various types of more common sarcomas

osteosarcoma liposarcoma leiomyosarcoma rhabdomyosarcoma malignant fibrous histiocytoma fibrosarcoma synovial sarcoma angiosarcoma chondrosarcoma

Table 2-2 The Biology of Cancer (© Garland Science 2007)

Figure 1.3: The most common sarcomas.

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... Leukemias and lymphomas are cancers comprising aberrant growth of blood cells ... Hematopoietic malignancies consist of malignancies of the blood, including **erythrocytes**, plasma cells, and **lymphocytes**. **leukemias** are liquid tumors and consist of uncontrolled growth of white blood cells throughout the bloodstream. **lymphomas** are tumors made from cells of lymphoid lineages that aggregate in lymph nodes to form solid masses. The most common **hematopoietic** malignancies are shown in Figure 1.4.

carcin/o: cancer

-oma: tumor, mass, swelling

squamous cell: a type of epithelial cell that is flat and forms a single-cell layer

aden/o: gland

carcin/o: cancer

-oma: tumor, mass, swelling

sarc/o: flesh

-oma: tumor, mass, swelling

mesenchymal: related to mesenchyme, i.e., connective tissue, bone, cartilage.

erythr/o: red

-cyte: cell

lymph/o: lymph

-cyte: cell

leuk/o: white

-emia: blood condition

lymph/o: lymph

-oma: tumor, mass, swelling

hemat/o: blood

-poiesis: creation

1.2. TUMOR LEVEL: DYSPLASIA, INVASION, AND METASTASIS

Table 2.3 Various types of more common hematopoietic malignancies

acute lymphocytic leukemia
acute myelogenous leukemia
chronic myelogenous leukemia
chronic lymphocytic leukemia
multiple myeloma
non-Hodgkin's lymphoma^a
Hodgkin's disease

^aThe non-Hodgkin's lymphoma types, also known as lymphocytic lymphomas, can be placed in as many as 15–20 distinct subcategories, depending upon classification system.

Table 2.3 The Biology of Cancer © Garland Science 2007

Figure 1.4: The most common hematopoietic malignancies.

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... Neuroectodermal tumors are tumors of the nervous system ... Neuroectodermal tumors arise from cells from the nervous system and comprise approximately 1% of clinical tumors. The most common neuroectodermal tumors are shown in Figure 1.5.

Table 2.4 Various types of neuroectodermal malignancies

glioblastoma multiforme
astrocytoma
meningioma
neurinoma
retinoblastoma
neuroblastoma
ependymoma
oligodendroglioma
medulloblastoma

Table 2.4 The Biology of Cancer © Garland Science 2007

Figure 1.5: The most common neuroectodermal tumors.

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..... Cancer is treated with surgery, radiation, and medicine

The tools we use to treat cancer include surgery (cutting out cancerous cells), radiation (damaging cancer cells so they die), and medicine (slowing down or killing cancer cells). As we discuss oncogenic processes, these will naturally lead to discussion of the expected effects of radiation and medicine on cancer cells. Further, as we discuss metastasis, this will naturally lead to discussion of when surgery will be effective.

..... Engineers develop tools for diagnosing and treating cancer

Engineers have many roles to play in cancer. These include designing physical systems to better simulate cancer systems, designing tools to detect cancer or cancer cells, and designing tools for treating cancer.

1.2

Tumor level: dysplasia, invasion, and metastasis

At the tumor level, we are interested in how tumor masses grow, what their shape, structure, growth, invasiveness, and spreading properties are, and how different cells interact with

1.2. TUMOR LEVEL: DYSPLASIA, INVASION, AND METASTASIS

each other to give rise to tumor behavior. We are also interested in the processes by which tumors affect nearby tissues.

.....
 Tumors arise from normal tissues and occur in many varied host tissues

Tumors derive from normal tissues. The primary tumor is the tumor from which the cancer originates, and we refer to cancer types by the tissue in which the first tumor was found. Thus liver cancer denotes cancer that started in the liver, even if this cancer is later found at another location in the body. Cancer is widely varied in many ways, including the nature of the host tissue, and cancers from different primary tissue sources behave differently. Figure 1.6 shows five-year survivals for many different cancers, highlighting the huge difference between cancers.

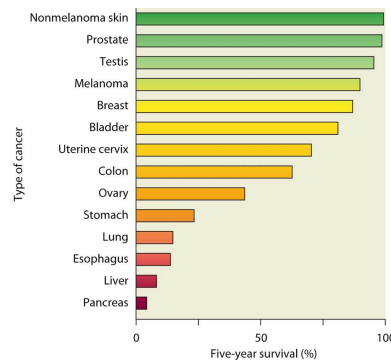


Figure 1.6: Five-year survival rates 1995–2000 by organ of origin.

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The word tumor refers to an aberrant cell mass. This mass comes from abnormal cell growth, and this abnormal cell growth is described with a number of different terms.

.....
 Hyperplasia leads to increased cell number

Hyperplasia is the increase in local cell number associated with deregulated proliferation. Hyperplasia implies, though, that the cells themselves appear normal. **hyperplasia** is typically the first step in tumor growth.

hyper-: increased or excessive

-plasia: growth

.....
 Dysplasia leads to aberrant cell organization and proliferation

dysplasia is the next step in tumor growth. This typically implies that cells appear abnormal and/or are in abnormal locations microscopically.

dys-: difficult or aberrant

-plasia: growth

.....
 Neoplasia implies disparate growths of cells

neoplasia is the next step in tumor growth. This typically implies that cells appear abnormal and abnormal collections of cells exist.

neo-: new

-plasia: growth

.....
 Invasion leads to local propagation of malignant cells

Invasiveness—the tendency for cancer cells to move locally – is a hallmark of cancer cells. **benign** tumors are those that invade locally but do not leave the host tissue.

benign: non-invasive i.e., localized to a specific area of tissue

.....
 Metastasis leads to distant propagation of malignant cells

Cells that invade other tissue and spawn **metastases** (remote, secondary tumors) are termed malignant. Cancer cells are **malignant** cells.

metastases: secondary tumors that form when cells from a primary tumor spread to remote parts of the body

.....
 Cancer is staged by microscopic appearance and degree of dissemination

staging is a system by which clinicians stage the size, invasiveness, and cellular characteristics of tumors. There are many systems and often multiple systems exist for a specific disease. Often, one system is used by surgeons, one by pathologists, one by medical oncologists. The TNM (Tumor–lymph Nodes–Metastasis) scheme identifies tumor size, whether it has invaded lymph nodes, and whether the tumor has metastasized. Other staging criteria are often focused on operability—i.e., would the patient die on the table if a tumor was removed. The correlation between tumor staging and survival is shown in Figure 1.7.

malignant: invasive i.e., spreading out from a specific area of tissue into different tissue types nearby (regional invasion) or remote (metastasis)

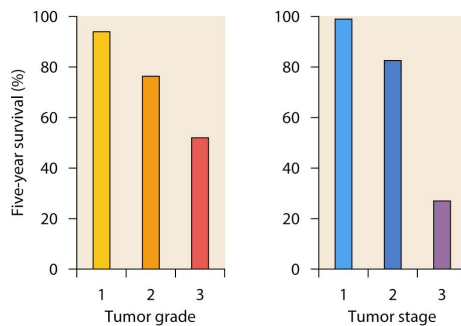


Figure 1.7: Right: Five-year survival rates 1995–2000 by tumor stage for breast cancer.

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.....
 Engineers can simulate tumors to study cancer

In coming chapters, we will see how tumor growth models can help us understand how tumors grow, and can inform how tumors are treated, for example from the standpoint of how drugs or radiation should be dosed.

.....
 Engineers can monitor metastatic processes to study cancer

Metastasis is fundamentally a transport problem, requiring that cells break away from a tumor, spread via lymph, blood, or other routes, find a home site, and then stabilize to form

1.3. CELL LEVEL: CELL CYCLE, CELL SURVIVAL, DNA DAMAGE, IMMUNOLOGY

a secondary tumor. Thus transport models will help us understand why liver and bone, for example, are common metastatic sites.

Engineers can model transport of therapeutics in the body and develop drug delivery approaches to improve therapeutic delivery

The most common routes of drug delivery (IV injection and oral dosing) require that the drug get from the blood to the tumor (in both cases) and from the digestive system to the blood (in the case of oral drugs). Thus the interaction between tumors and the circulatory system is critical in predicting how medical intervention can affect cancer.

1.3
Cell level: cell cycle, cell survival, dna damage, immunology

Healthy multicellular organisms exert tight control on each individual cell in the body. Cancer is a disease in which cells evade this control and proliferate uncontrollably, and most cancer study in recent decades has been at the cellular level. Engineers and physicists particularly have the potential to impact cancer research in its expansion to tissue and body levels.

Cancer cells proliferate abnormally

As shown in Figure 3.1, there are multiple types of new tissue growth, namely **hypertrophy**, **hyperplasia**, **dysplasia**, and **neoplasia**. In different ways, these growth types all relate to (or can relate to) different aberrant cell behavior. Hypertrophy describes an increase in cell size; hyperplasia describes an increase in cell number. These can be normal behavior (for example muscle growth is hypertrophy, healing is hyperplasia). Dysplasia denotes aberrant, disorganized growth. Neoplasia denotes disorganized growth with an increase in the number of dividing cells. Neoplasia implies a tumor. Neoplasia is the result of a loss of balance between cell growth and death.

Cancer cells have aberrant cell cycles and respond aberrantly to growth factors

Normal cells grow and divide only when stimulated by growth factors (e.g., **EGF** and **PDGF**) from their environment. This ensures that normal cells grow only when instructed to do so. The signals from growth factors are transduced to the interior of the cell by growth factor receptors, for example **EGFR** and **PDGFR**. Cancer cells become aberrant when their growth becomes independent of these external signals, because the growth factor receptors respond erroneously or because the cell makes its own growth factors. Normal and aberrant growth factor signaling is shown in Figure 3.4.

Cancer cells do not self-destruct when they should

Healthy cells have a tightly regulated program for when they should die, and most cell death in humans is programmed, purposeful death. **necrosis**, uncontrolled death, is relatively uncommon and usually occurs only upon injury. In contrast, **apoptosis** is occurring

hyper- : increased or excessive
-trophy : nourishment, development
hyper- : increased or excessive
-plasia : growth
dys- : difficult or aberrant
-plasia : growth
neo- : new
-plasia : growth
EGF : epidermal growth factor
PDGF : platelet-derived growth factor
EGFR : epidermal growth factor receptor
PDGFR : platelet-derived growth factor receptor

necr/o : death
-osis : (usually abnormal) condition
necrosis : Unregulated cell death
apoptosis : Cell suicide activated by external signaling or internal detection of cell damage

1.3. CELL LEVEL: CELL CYCLE, CELL SURVIVAL, DNA DAMAGE, IMMUNOLOGY

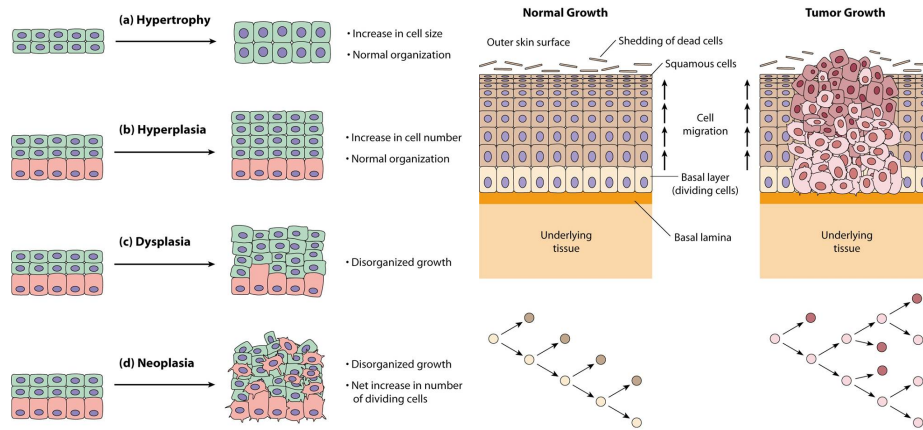


Figure 1.8: Left: Four types of new tissue growth, ranging from most benign to most malignant. Color code represents cell capability to divide (green: cannot divide; red: can divide). Right: comparison between healthy growth and tumor growth in skin. Lighter shade denotes capability to divide.

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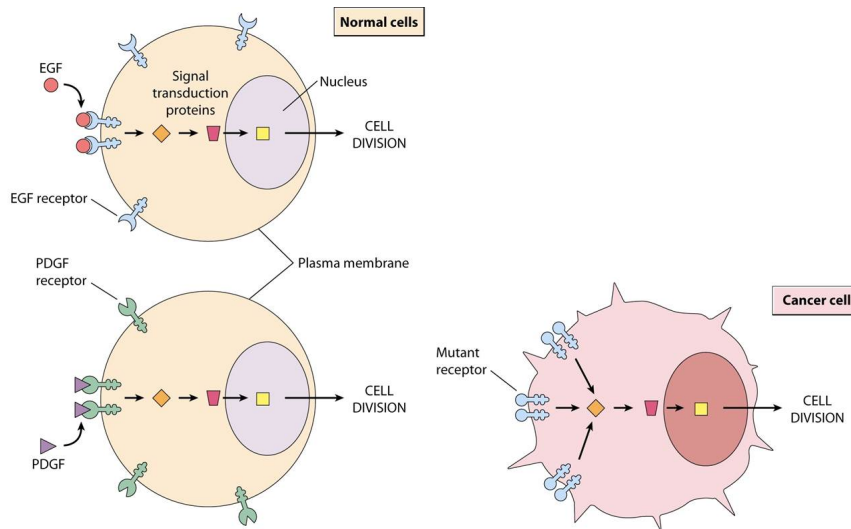


Figure 1.9: Growth factor signaling. Left: two cells show normal response of growth factor receptors to growth factors **EGF** and **PDGF**, respectively. Right: a cell with a mutant receptor that is always active, leading to uncontrolled growth even in the absence of growth factors.

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1.3. CELL LEVEL: CELL CYCLE, CELL SURVIVAL, DNA DAMAGE, IMMUNOLOGY

constantly in the body and is a central part of both development and normal operation. Cells kill themselves when they are not needed or are defective. Cells kill themselves when they are infected with pathogens or when their DNA is found to be defective. Cells somehow in the wrong place (unable to bind in a way they expect, not receiving **paracrine** or **endocrine** signals they expect) kill themselves.

Cancer cells, in contrast, typically have a disrupted apoptotic program and they do not invoke apoptosis. This has an important effect, especially when it comes to the cellular DNA. Because cells with DNA mutations kill themselves, the genetic integrity of cells is maintained. However, cancer cells often have mutations in the proteins that check DNA integrity and induce apoptosis when this integrity is compromised. Because of this, cancer cells fail to self-destruct when they should, and cancer cells can acquire significant disruptions in their DNA.

para-: around, nearby
-crine: signal
endo-: within
-crine: signal
endocrine: relating to secretion in to the bloodstream

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Cancer cells have profoundly disrupted genetic information

DNA mutations arise spontaneously, as DNA replication is not perfect. Further, many mutagens cause mutations to become much more common. Figure 3.15 shows several simple DNA mutation mechanisms. In addition to small-scale mutations, cancer

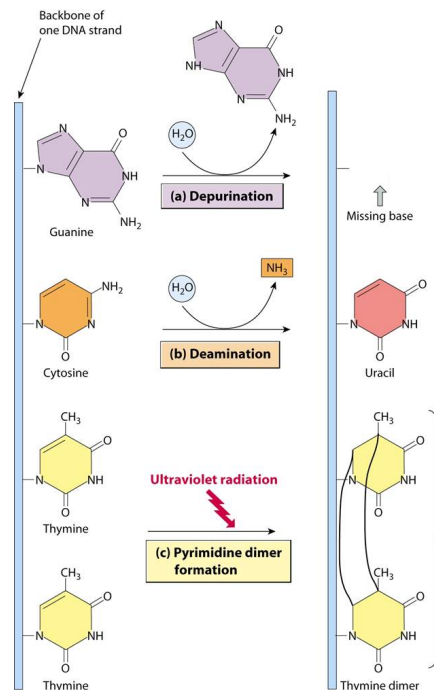


Figure 1.10: (a) depurination and (b) deamination are spontaneous mutations stemming from DNA–water interactions. (c) UV light dimerizes pyrimidines.

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cells exhibit gross chromosomal abnormalities—unlike healthy cells, which are **diploid**, they often are **aneuploid**, meaning that they have chromosome copies other than two, and often incorrect repair of DNA leads to parts of different chromosomes being attached to

di-: two
-ploid: having a DNA copy number state
an-: against, not
eu-: good, normal
-ploid: having a DNA copy number state

1.3. CELL LEVEL: CELL CYCLE, CELL SURVIVAL, DNA DAMAGE, IMMUNOLOGY

each other—what is called chromosomal translocation. A classic example of this is the Philadelphia chromosome, an exchange of chromosomes 9 and 22 that leads to **chronic myelogenous leukemia**. Figure 3.16 shows differences in **karyotypes** between healthy and cancerous cells.

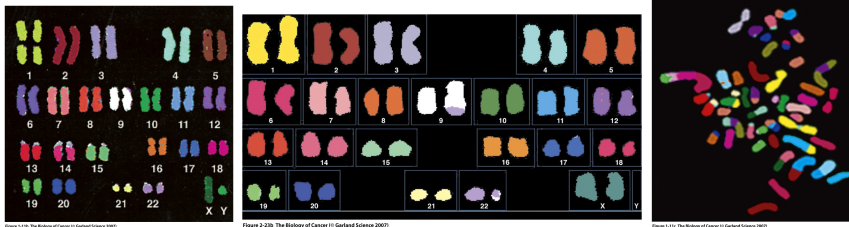


Figure 1.11: Left: Diploid **karyotype** of a normal human cell. Middle: karyotype of chronic myelogenous leukemia patient with a 9q+,22q- translocation. Note exchange of white and purple regions indicating chromosomal translocation. Right: aneuploid karyotype of a breast cancer cell. Note numerous translocations indicated by the varied colors in each chromosome.

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kary/o: nucleus

-type: type

.....
 Cancer cells exhibit molecular changes that change adhesiveness, paracrine signaling, and angiogenesis

Cancer cells exhibit novel molecular changes. One is a reduction in cell adhesion proteins and gap junction proteins. These lead cancer cells to be less adhesive. Cancer cells produce proteases that help enzymatically degrade their surroundings, and secrete factors that induce **angiogenesis**.

angi/o: vessels

gen-: creation

.....
 The aberrations that lead to cancer also lead to other pathologies in other contexts

-esis: condition/action/process

Cancer is a system with complicated and manifold causes but constrained by the phenotypic observation of localized uncontrolled growth that is invasive. Many of the phenomena that lead to cancer could lead to other system failures—death during embryonic development, etc. The term *cancer* is used to describe the unique processes that allow an organism to function healthily for some time before a process of localized uncontrolled growth leads to disease.

.....
 The properties of cancer are often summarized in terms of a number of hallmarks of cancer

Cancer can be described as a disease of cells that are independent of growth and antigrowth signals, that evade apoptosis, and retain limitless replicative potential. These cells form tumors that invade and metastasize, sustaining angiogenesis in response to local hypoxia. These properties are summarized in Figure 1.12.

1.3. CELL LEVEL: CELL CYCLE, CELL SURVIVAL, DNA DAMAGE, IMMUNOLOGY

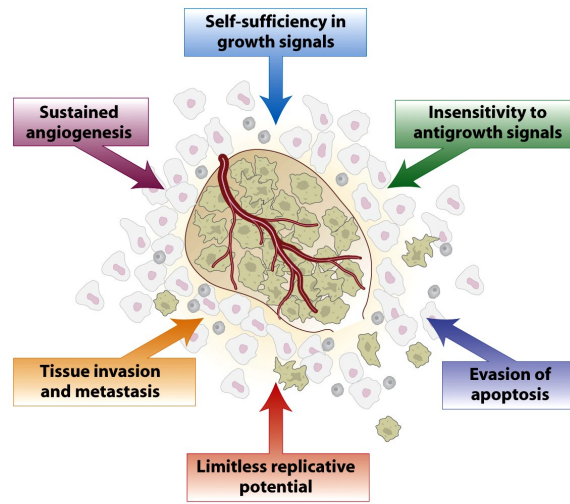


Figure 25-1
Molecular Cell Biology, Sixth Edition
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Figure 1.12: Hallmarks of cancer.

Image from Lodish, *Molecular Biology of the Cell* used under one-time fair academic use guidelines during Spring 2013 only. DO NOT DUPLICATE OR DISTRIBUTE.

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Engineers can measure cellular properties to study cancer

A key component of the course project will encourage a subset of the class to explore cellular properties, how these can be indicative of cancer, and how these are affected by engineering intervention.

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Engineers can take advantage of cancer cell properties to identify cancer cells

Further, cancer cell properties and tumor properties can be used to identify cancer for diagnostic and therapeutic purposes.