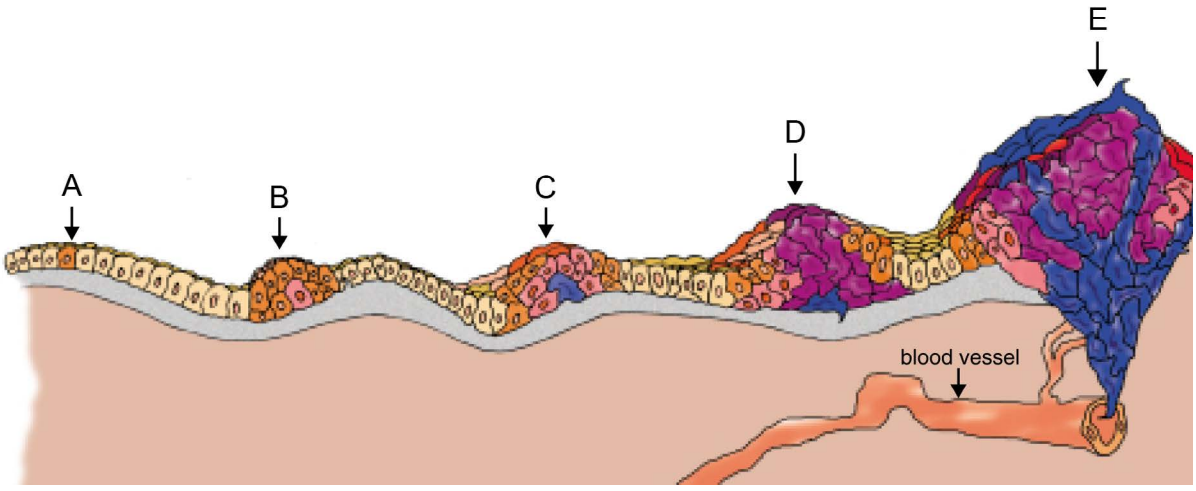
Understanding Cancer

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. There are more than 100 different types of cancer. Cancer is a disease caused by genetic changes that develop over time. Although cancer can develop in virtually any of the body's tissues and each type of cancer has its unique features, the basic processes that produce cancer are quite similar in all forms of the disease.

Cancer begins when a cell breaks free of the normal restraints on cell division and begins to follow its own agenda for proliferation (**Figure 2**). All the cells produced by division of this first, ancestral cell and its progeny also display inappropriate proliferation. A **tumor**, or mass of cells, formed of these abnormal cells may remain within the tissue in which it originated (a condition called **in situ cancer**). However, one of the central characteristics of a cancer cell is its ability to invade nearby tissue and spread to other parts of the body.

Cancers can spread throughout the body by two mechanisms: invasion and metastasis. **Invasion** refers to the direct migration and penetration by cancer cells into neighboring tissues. **Metastasis** refers to the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and then invade normal tissues elsewhere in the body. **Malignant** tumors are capable of spreading by invasion and metastasis, and, by definition, the term "cancer" applies only to malignant tumors. Tumors threaten an individual's life when their growth disrupts the tissues and organs needed for survival.

Figure 2. *The stages of tumor development. A malignant tumor develops over time, as shown in this diagram.* ***A.*** *The tumor begins to develop when a single cell's DNA becomes altered, or mutated. We do not know the exact number of mutations required for a normal cell to become a fully malignant cell, but it is probably fewer than 10. The accumulation of mutations can transform a normal cell into a cancerous one.* ***B.*** *The altered cell and its descendants grow and divide rapidly, resulting in a condition called* ***hyperplasia****. At some point, one of these cells experiences another mutation that further increases its tendency to divide.* ***C.*** *This cell's descendants divide excessively and look abnormal, a condition called* ***dysplasia****. As time passes, one of the cells experiences yet another mutation.* ***D****. This cell and its descendants are very abnormal in both growth and appearance. If the tumor that has formed from these cells is still contained within its tissue of origin, it is called in situ, or stage 0, cancer. In situ cancer may remain contained indefinitely.* ***E****. If some cells experience additional mutations that allow the tumor to invade neighboring tissues and to shed cells into the blood or lymph, the tumor is said to be malignant. The escaped cells may establish new tumors (metastases) at other locations in the body.*



What happens to cause a cell to become cancerous? Forty years ago, scientists could not offer a coherent answer to this question. They knew that cancer arose from cells that began to proliferate uncontrollably within the body, and they knew that chemicals, radiation, and viruses could trigger this change. But exactly how it happened was a mystery.

Research across the past three to four decades, however, has revolutionized our understanding of cancer. In large part, this success was made possible by the development and application of the techniques of molecular biology, techniques that enabled researchers to probe and describe features of individual cells in ways unimaginable a century ago. Today, we know that cancer is a disease of molecules and genes, and we have even identified many of the molecules and genes involved. In fact, our increasing understanding of these genes is making possible the development of exciting new strategies for avoiding, forestalling, and even correcting the changes that lead to cancer.

Unraveling the Mystery of Cancer

People have likely wondered about the cause of cancer for centuries. Its name derives from an observation by Hippocrates more than 2,300 years ago that the long, distended veins that radiate out from some breast tumors look like the limbs of a crab. From that observation came the term *karkinoma* in Greek and later, *cancer* in Latin.

With the work of Robert Hooke in the 1600s, and then Rudolf Virchow in the 1800s, came the understanding that living tissues are composed of cells, and that all cells arise as direct descendants of other cells. Yet this understanding raised more questions about cancer than it answered. Scientists began to ask from what kinds of normal cells cancer cells arise, how cancer cells differ from their normal counterparts, and what events promote the proliferation of these abnormal cells; physicians began to ask how cancer could be prevented or cured.

Clues from epidemiology. One of the most important early observations that people made about cancer was that its incidence varies between different populations. For example, in 1775, an extraordinarily high incidence of scrotal cancer was described among men who worked as chimney sweeps as boys. In the mid-1800s, lung cancer was observed at alarmingly high rates among pitchblende miners in Germany. By the end of the 19th century, using snuff and cigars was thought by some physicians to be closely associated with cancers of the mouth and throat.

These observations and others suggested that the origin or causes of cancer may lie outside the body and, more important, that cancer could be linked to identifiable and even preventable causes. These ideas led to a widespread search for agents that might cause cancer. One early notion, prompted by the discovery that bacteria cause a variety of important human diseases, was that cancer is an infectious disease. Another idea was that cancer arises from the chronic irritation of tissues. This view received strong support with the discovery of X-rays in 1895 and the observation that exposure to this form of radiation could induce localized tissue damage, which could lead in turn to the development of cancer. A conflicting view, prompted by the observation that cancer sometimes seems to run in families, was that cancer is hereditary.

Such explanations, based as they were on fragmentary evidence and incomplete understanding, helped create the very considerable confusion about cancer that existed among scientists well into the mid-20th century. The obvious question facing researchers—and no one could seem to answer it—was how factors as diverse as these could all cause cancer. Far from bringing science closer to understanding cancer, each new observation seemed to add to the confusion.

Yet each new observation also contributed to scientists' eventual understanding of the disease. For example, the discovery in 1910 that a defined, submicroscopic agent isolated from a chicken tumor could induce new tumors in healthy chickens showed that a tumor could be traced simply and definitively back to a single cause. Today, scientists know this agent as Rous sarcoma virus, one of several viruses that can cause cancer. Although viruses do not cause

the majority of human cancers, their intensive study focused researchers' attention on the central role cellular genes play in the development of the disease.

Likewise, investigations into the association between cancer and tissue damage, particularly that induced by radiation, revealed that while visible damage sometimes occurs, something more subtle happens in cells exposed to cancer-causing agents. One clue to what happens came from the work of Hermann Muller, who noticed in 1927 that exposing fruit flies to X-rays often resulted in mutant offspring. Might the two known effects of X-rays, promotion of cancer and genetic mutation, be related to one another? And might chemical **carcinogens** (cancer-causing agents) induce cancer through a similar ability to damage genes?

Support for the idea that genetic damage underlies cancer came from the work of Bruce Ames and others, who showed in 1975 that compounds known to be potent carcinogens were generally also potent **mutagens** (mutation-inducing agents), and that compounds known to be only weak carcinogens were only weak mutagens. Although scientists know today that many chemicals do not follow this correlation precisely, this initial, dramatic association between mutagenicity and carcinogenicity had widespread influence on the development of a unified view of the origin and development of cancer.

Finally, a simple genetic model, proposed by Alfred Knudson in 1971, provided a compelling explanation for the origins of retinoblastoma, a rare tumor that occurs early in life. Knudson's model also provided a convincing way to reconcile the view of cancer as a disease produced by external agents that damage cells with the observation that some cancers run in families. The model states that children with sporadic retinoblastoma (children whose parents have no history of the disease) are genetically normal at the moment of conception but experience two somatic mutations (mutations that occur in nonreproductive cells) that lead to the development of an eye tumor. Children with familial retinoblastoma (that is, their parents have a history of the disease) already carry one mutation at conception and thus must experience only one more mutation to reach the doubly mutated configuration required for a tumor to form. In familial retinoblastoma, each retinal cell is already "primed" for tumor development, needing only a second mutational event to trigger the cancerous state. The difference in probabilities between the requirement for one or two mutational events happening randomly explains why in sporadic retinoblastoma, the affected children have only one tumor focus in one eye, while in familial retinoblastoma, the affected children usually have multiple tumor foci growing in both eyes.

Although it was years before Knudson's explanation was confirmed, it had great impact on scientists' understanding of cancer. Retinoblastoma and, by extension, other familial tumors appeared to be linked to the inheritance of mutated versions of growth-suppressing genes. This idea led to the notion that cells in sporadically arising tumors might also have experienced damage to these critical genes as the cells moved along the path from the normal to the cancerous state.

Applying advances in cell and molecular biology, scientist are now melding genomics and epidemiology to further explore why some people develop cancer while others do not. Scientists are harnessing the power of new genomic technologies through epidemiologic studies designed to uncover gene variants that contribute to cancer susceptibility. Findings from family studies have formed the basis for our understanding of many **high-penetrance** cancer-causing mutations. These rare mutations give unprecedented insights into carcinogenic mechanisms but are responsible for only a small proportion of all cancers. Most cancer risk is believed to be due to gene-environment interactions involving **low-penetrance** but common genetic variants or **single-nucleotide polymorphisms** (or SNPs, pronounced "snips")—specific sites within a human genome at which some individuals will have one nucleotide present while other individuals will have a different one.

Cancer-associated mutations—whether somatic or inherited, whether SNPs or larger genetic changes—alter key cellular functions. A wide

variety of mutations seems to be involved in the development of cancer. Even mutations in regions of DNA that do not code for proteins can result in under- or overexpression of proteins needed for normal functioning. Other genetic mutations may cause important "checkpoint" proteins to malfunction. Collectively, these mutations can convert a cell's genome from normal to cancerous.

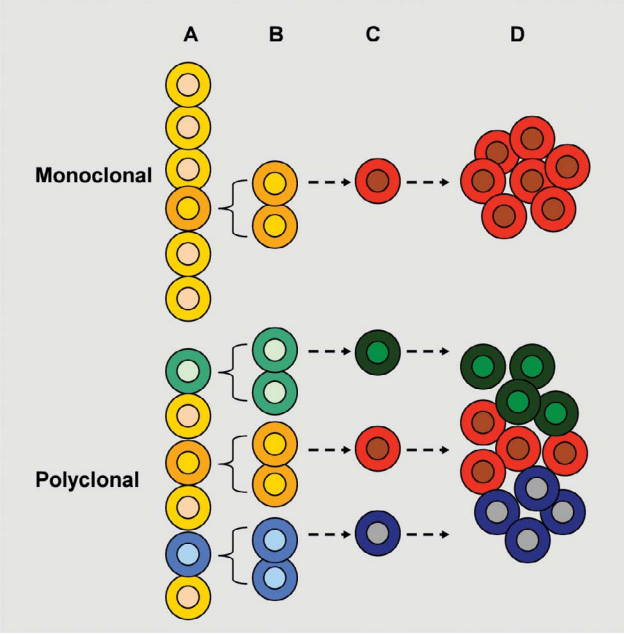
Clues from cell biology. Another field of study that has contributed to scientists' growing understanding of cancer is cell biology. Cell biologists studied the characteristics of cancer cells through observations in the laboratory and by inferences from their appearance in the whole organism. Not unexpectedly, these investigations yielded a wealth of information about normal cellular processes. But they also led to several key understandings about cancer, understandings that ultimately allowed scientists to construct a unified view of the disease.

One such understanding is that cancer cells arise from the body's own tissues. Scientists identified the origin of cancer cells from attempts to transplant tissues from one person to another. Such transplants work well between identical twins, but not as well when the people involved are more distantly or not related. The barrier to successful transplantation exists because the recipient's immune system can normally distinguish between "self" and "nonself"—cells of foreign origin. One practical application of this discovery is that tissues can be classified as matching or nonmatching before a doctor attempts to graft a tissue or organ into another person's body. Such tissue-typing tests, when done on cancer cells, reveal that the tumor cells of a particular cancer patient are always of the same transplantation type as the cells of normal tissues located elsewhere in the person's body. Tumors, therefore, arise from one's own tissues, not from cells introduced into the body by infection from another person.

Furthermore, virtually all malignant tumors are monoclonal in origin—that is, they are derived from a single ancestral cell that somehow underwent conversion from a normal to a cancerous state. These insights, as straightforward as they seem, were surprisingly difficult to reach. How could biologists describe the cell pedigree of a mass of cells that eventually is recognized as a tumor?

Two distinct scenarios might explain how cancers develop within normal tissues. In the first, only one cell experiences the original transformation from a normal cell to a cancerous cell, and all the cells in the tumor are descendants of that cell (**Figure 3**). In the second scenario, many individual cells become cancerous, and the resulting tumor represents the descendants of these original cells. In this case, the tumor is **polyclonal** in nature.

Figure 3. *Each cell, when it divides, generates two identical progeny cells. So, when a cell acquires a mutation* ***(A)****, it passes that mutation on to its progeny during cell growth and division* ***(B)****. Because cells with cancer-linked mutations tend to proliferate more rapidly than normal cells, cellular candidates for additional mutations grow in number. Mutations continue to accumulate and are inherited by descendant cells. If one cell finally acquires enough of the right kind of mutations to become cancerous* ***(C)****, subsequent cancer cells will be derived from that one single transformed cell. Most—if not all—human cancers* ***(D)*** *appear to be monoclonal, that is, they originate from a single parent cell.*



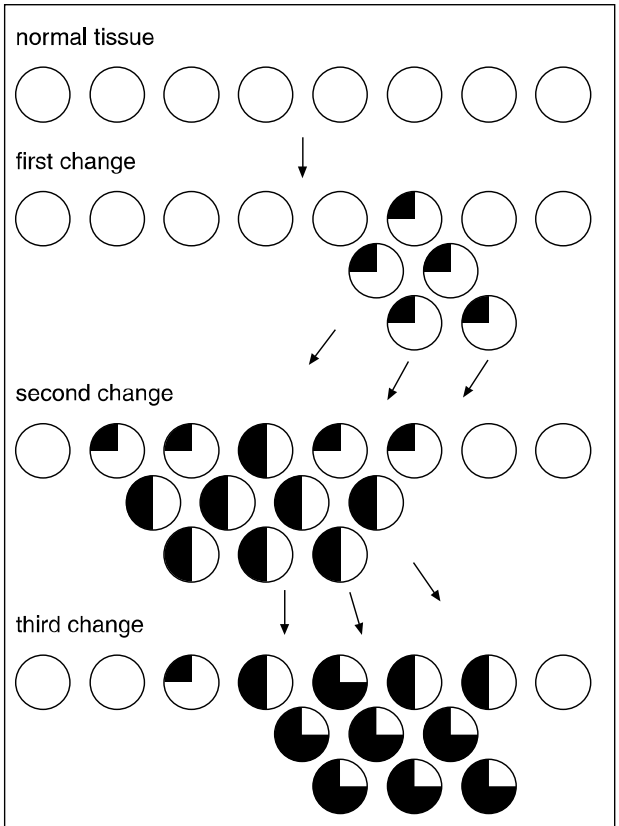
The current view is that the polyclonal origin of malignant tumors is the exception rather than the rule, but direct evidence of this was difficult to acquire because most tumor cells lack obvious distinguishing marks that scientists can use to demonstrate their clonal relationship. There is, however, one cellular marker that scientists can use as an indication of such relationships: the inactivated X chromosome that occurs in almost all body cells of human females. X-chromosome inactivation occurs randomly during female embryonic development. Because the inactivation is random, a female is like a mosaic in terms of the X chromosome, with different copies of the X (either the maternal or paternal X) turned on or off in different cells of the body. Once inactivation occurs in a cell, all the future generations of cells coming from that original cell also will have the same chromosome inactivated. The observation that all the cells within a given tumor invariably have the same X chromosome inactivated suggests that all cells in the tumor must have descended from a single ancestral cell.

The recent identification in solid tumors and hematologic cancers of cells with stem cell–like properties has generated considerable excitement in the cancer research community. These cancer stem cells (or cancer-initiating cells) can both self-renew to maintain the population of stem cells and produce the more-differentiated cells that make up the bulk of a tumor. Scientists now believe that cancer stem cells may play a role in the formation, recurrence, and metastasis of many solid and hematologic cancer types and may present a target that must be eradicated to potentially produce a cure (NCI, 2007a).

Cancer, then, is a disease in which a single normal body cell undergoes a genetic transformation into a cancer cell. Even this picture, although accurate in its essence, does not represent a complete description of the events involved in tumor formation. Additional research revealed that as a tumor develops, the cells of which it is composed become different from one another as they acquire new traits and form distinct subpopulations of cells within the tumor. As shown in **Figure 4**, these changes allow the cells that incorporate them to compete with increasing success against cells that lack the full set of changes. The development of cancer, then, occurs as a result of a series of clonal expansions from a single ancestral cell. This cell and its descendants proliferate to produce the population of cells that we recognize as a tumor, and tumors produce the symptoms that an individual experiences as cancer.

A second critical understanding that emerged from studying the biology of cancer cells is that these cells show a wide range of important differences from normal cells. For example, cancer cells are genetically unstable and prone to rearrangements, duplications, and deletions of pieces of their chromosomes that cause their progeny to display unusual traits.

Figure 4. *A series of changes—successive clonal expansions—leads to tumor formation. This figure shows three such changes; the development of most cancers likely involves more than three. The relative numbers of each type of cell indicate competitive success.*



Source: Modified from Varmus, H., & Weinberg, R.A. 1993. *Genes and the biology of cancer.* New York: Scientific American Library.

Cancerous cells also look and act differently from normal cells. In most normal cells, the nucleus is only about one-fifth the size of the cell; in cancerous cells, the nucleus may occupy most of the cell's volume. Tumor cells also often lack the differentiated traits of the normal cell from which they arose. Whereas normal secretory cells produce and release mucus, cancers derived from these cells may have lost this characteristic. Likewise, epithelial cells usually contain large amounts of keratin, but the cells that make up skin cancer may no longer accumulate this protein in their cytoplasms.

The key difference between normal and cancerous cells, however, is that cancer cells have lost the restraints on growth that characterize normal cells. When grown in laboratory culture, cancer cells demonstrate a variety of unusual characteristics, including a lack of contact inhibition (growth arrest when cells come into contact with each other), a reduced dependence on the presence of growth factors in the environment, and, often, the ability to proliferate indefinitely.

Significantly, a large number of cells in a tumor are engaged in mitosis, whereas mitosis is a relatively rare event in most normal tissues. Cancer cells also do not interact normally with other cells in their environment. Tumor cells can send signals to neighboring cells that may establish a more-favorable environment for additional tumor growth and progression. These signals may encourage the growth of new blood vessels; stimulate the production of proteins that disrupt cell adhesion, promote cell growth, or prevent programmed cell death (**apoptosis**); and/or suppress the immune response.

Therefore, a critical point that has emerged from research is the notion that a tumor is not simply a ball of cancer cells but, rather, functions somewhat like an organ—with vasculature, supporting tissue (or **stroma**), enzymes, proteins, growth factors, and **cytokines**. Understanding the tumor necessitates understanding its **tumor microenvironment**. The tumor microenvironment plays a critical role in tumor initiation and progression and may be an important factor in developing therapeutic approaches. The tumor microenvironment influences the growth of the tumor and its ability to progress and metastasize. It can also limit the access of therapeutics to the tumor, alter drug metabolism, and contribute to the development of drug resistance. Because of their roles in all the stages of tumor development, elements of the tumor microenvironment represent attractive therapeutic targets. Manipulating tumor-stromal interactions may be important in preventing or reversing malignant conversion and reestablishing normal control mechanisms.

A unified view. By the mid-1970s, scientists started to develop the basis of our modern molecular understanding of cancer. In particular, the relationship Ames and others had established between mutagenicity and carcinogenicity provided substantial support for the idea that chemical carcinogens act directly through their ability to damage cellular genes. This idea led to a straightforward model for the initiation of cancer: Carcinogens induce mutations in critical genes, and these mutations direct the cell in which they occur, as well as all of its progeny cells, to grow abnormally. The result of this abnormal growth appears—sometimes years later—as a tumor. The model could even explain the observation that cancer sometimes appears to run in families. If cancer is caused by mutations in critical genes, then people who inherit such mutations would be more susceptible to cancer's development than people who do not.

As exciting as it was to see a unified view of cancer begin to emerge from the earlier confusion, cancer researchers knew their work was not finished. The primary flaw in their emerging explanation was that the nature of these cancer-causing mutations was unknown. Indeed, the very existence of such mutations had yet to be proven. Evidence from work with cancer-causing viruses suggested that only a small number of genes were involved in tumor development, and evidence from cell biology pointed to genes that normally control cell division. But now scientists asked new questions: Exactly which genes are involved? What are their specific roles in the cell? How do their functions change as a result of mutation?

It would take another 20 years and a revolution in the techniques of biological research to answer these questions. However, today our picture of the causes and development of cancer is so detailed that scientists find themselves in the extraordinary position of not only knowing many of the genes involved but also being able to aim prevention, detection, and treatment efforts directly at these genes.

Cancer as a Multistep Process

A central feature of today's molecular view of cancer is that cancer does not develop all at once but rather does so over time, as a succession of genetic changes. Each change enables precancerous cells to acquire some of the traits that together allow the malignant growth of cancer cells. It is clear that the normal cellular processes that control the cell cycle, cell survival, and the elimination of unnecessary or damaged cells are altered during tumorigenesis.

Two categories of genes play major roles in triggering cancer: **proto-oncogenes** and **tumor-suppressor genes**. In their normal forms, proto-oncogenes are involved in normal cellular processes that encourage cell division. Tumor-suppressor genes, on the other hand, play a role in inhibiting cell division, in promoting apoptosis, or both. Together, proto-oncogenes and tumor-suppressor genes coordinate the regulated growth that normally ensures that each tissue and organ in the body maintains a size and structure that meets the body's needs. In fact, most proto-oncogenes and tumor-suppressor genes play key roles in regulating cellular growth and survival during embryonic development. Mutations in these genes account for much of the uncontrolled cell division and evasion of apoptosis that occurs in human cancers (Table 8).

The role of oncogenes. Most proto-oncogenes code for proteins involved in molecular pathways that receive and process growth-stimulating signals from other cells in a tissue. Typically, such signaling begins with the production of a growth factor, a protein that stimulates cell division. Growth factors move through the spaces between cells and attach to specific receptor proteins located on the surfaces of neighboring cells. When a growth-stimulating factor binds to such a receptor, the receptor conveys a stimulatory signal to proteins in the cytoplasm. These proteins transmit stimulatory signals to other proteins in the cell until the division-promoting message reaches the cell's nucleus and activates a set of genes that help move the cell through its growth cycle. Most of the known oncogenes are proto-oncogenes that have been altered or mutated in such a way that they promote cell growth in an abnormal or uncontrolled fashion.

Table 8. Examples of proto-oncogenes and tumor-suppressor genes and some of the human cancers associated with mutations in these genes.

Gene Type	Related Cancers
Proto-oncogene *bcl-2*	B-cell lymphoma
Proto-oncogene *HER2/neu* (*erbB-2*)	Breast and ovarian cancers
Proto-oncogene *c-Src*	Colorectal cancers
Proto-oncogene *c-Myc*	Burkitt lymphoma
Tumor-suppressor gene *BRCA1*, *BRCA2*	Breast and ovarian cancers
Tumor-suppressor gene *p53*	Brain tumors; skin, lung, and head and neck cancers
Tumor-suppressor gene *RB*	Retinoblastoma; bone, bladder, and breast cancers
Tumor-suppressor gene *APC*	Colorectal cancers

The protein products of oncogenes cause growth-promoting pathways to become overactive. As a result, the cell proliferates much faster than it would if the mutation had not occurred. Some oncogenes cause cells to overproduce growth factors. These factors can stimulate the growth of neighboring cells, but they may also drive excessive division of the cells that produced them. Other oncogenes produce aberrant receptor proteins that release stimulatory signals into the cytoplasm even when no growth factors are present in the environment. Still other oncogenes disrupt parts of the signaling cascade that occurs in a cell's cytoplasm causing the cell's nucleus to receive stimulatory messages continuously, even when growth factor receptors are not prompting them.

The role of tumor-suppressor genes. To become cancerous, cells must also break free from the inhibitory signals that normally counterbalance these growth-stimulating pathways. In normal cells, inhibitory messages flow to a cell's nucleus much like stimulatory messages do. But when this flow is interrupted, the cell can ignore these normally powerful inhibitory signals.

Some tumor-suppressor genes code for proteins that inhibit progression of the cell cycle. When such proteins are inactive or absent, these inhibitory pathways no longer function normally. Other tumor-suppressor genes appear to regulate the flow of signals through growth-stimulating pathways; when these genes do not function properly, such growth-promoting pathways may operate without normal restraint. Mutations in all tumor-suppressor genes, however, apparently inactivate critical tumor-suppressor proteins, depriving cells of this brake on cell division.

Most human cells contain two copies, or **alleles**, of each gene (with the exception of the sex chromosomes in males). When the alleles are identical, a person is **homozygous** for the trait that the gene encodes. For proto-oncogenes, it is important to note that when one allele of a particular proto-oncogene is converted (for example, through mutation) into an oncogene, the cell can experience the abnormal growth-promoting effects associated with that oncogene. However, if a cell contains only one inactive allele of a tumor-suppressor gene—and the other allele is still active—the active allele is usually sufficient to maintain normal growth-inhibiting functions associated with that gene and its protein product. Thus, in cases where a person is **heterozygous** for a particular tumor-suppressor gene—that is, they inherit one active and one inactive allele—then loss of **heterozygosity**, or the additional loss of the one functioning allele, is required for a complete loss of associated tumor-suppressor activity.

The body's back-up systems. In addition to the controls on proliferation, cells have at least three other systems that can help them avoid runaway cell division. The first of these is the DNA-repair system. This system operates in virtually every cell in the body, detecting and correcting errors in DNA. Across a lifetime, a person's genes are under constant attack, both by carcinogens in the environment and by chemicals produced in the cell itself. Errors also occur during DNA replication. In most cases, such errors are rapidly corrected by the cell's DNA-repair system. Should the system fail, however, the error (now a mutation) becomes a permanent feature in that cell and in all of its descendants.

The normally high efficiency of DNA repair is one reason why many years typically must pass before all the mutations required for cancer to develop occur together in one cell. Mutations in DNA-repair genes themselves, however, can undermine this repair system in a particularly devastating way. They damage a cell's ability to repair errors in its DNA. As a result, mutations appear in the cell (including mutations in genes that control cell growth) much more frequently than normal. For example, the *BRCA1* and *BRCA2* genes play a role in DNA repair, and mutations in them increase the risk of breast and ovarian cancers and possibly other cancers as well.

A second cellular back-up system prompts a cell to "commit suicide" by initiating apoptosis if some essential component is damaged or its control

system is deregulated. This observation suggests that tumors arise from cells that have managed to evade such death. One way of avoiding apoptosis involves the p53 protein, the product of a tumor-suppressor gene. In its normal form, this protein not only halts cell division, but induces apoptosis in abnormal cells; p53 is inactivated in many types of cancers.

The ability to avoid apoptosis contributes to cancer development. First, it contributes to the growth of tumors. Second, it makes cancer cells resistant to treatment. Scientists used to think that radiation and chemotherapeutic drugs killed cancer cells directly by harming their DNA. It is now known that even though these therapies do cause DNA damage, the resulting cell death is due to the damaged cancer cells actively killing themselves. This discovery suggests that cancer cells able to evade apoptosis will be less responsive to treatment than other cells.

A third back-up system limits the number of times a cell can divide, and so ensures that cells cannot reproduce endlessly. This system is governed by a counting mechanism that involves the DNA segments at the ends of chromosomes. Called **telomeres**, these segments shorten each time a chromosome replicates. Once the telomeres are shorter than a certain threshold length, they trigger an internal signal that causes the cell to stop dividing. If the cells continue dividing, the telomeres can be lost completely and adjacent DNA damaged. Because DNA ends lacking telomeres are also recognized as inappropriate DNA breaks, the cell repair mechanisms can fuse chromosomes together, a genetic crisis that is inevitably fatal to the cell.

Early observations of cancer cells grown in culture revealed that, unlike normal cells, cancer cells can proliferate indefinitely. An enzyme called telomerase, which systematically replaces the telomeric segments that are left off during each round of cell division, is absent from most mature cells but present in most cancer cells, where its action helps the cells proliferate endlessly.

The multistep development of cancer. Cancer, then, does not develop all at once as a massive shift in cellular functions resulting from a mutation in one or two wayward genes. Instead, it develops step-by-step, over time, as a result of the accumulation of many molecular changes, each contributing some of the characteristics that eventually produce the malignant state. The number of cell divisions that occur during this process can be astronomically large, and, as you might expect, the time frame involved can be very long—it can take decades to accumulate enough mutations to reach a malignant state. In addition, the rates of growth of tumors can vary, and it can take years for the tumors to be detectable.

Understanding cancer as a multistep process that occurs across long periods of time explains a number of long-standing observations. A key observation is the increase in cancer incidence with age. Most cases of cancer occur in people who have lived long enough to have experienced a complex and extended succession of genetic changes. In general, each event is rare. Therefore, it can take a long time for cancer to develop.

Understanding cancer in this way also explains the increase in cancer incidence in people who experience unusual exposure to carcinogens or who inherit predisposing mutations. Exposure to carcinogens increases the likelihood that certain harmful changes will occur, greatly increasing the probability of developing cancer during a normal life span. Similarly, inheriting a cancer-susceptibility mutation means that instead of that mutation being a rare event, it has already occurred, and not just in one or two cells, but in all of the body's cells. In other words, the process of tumor formation has leapfrogged over one of its early steps. Now, the accumulation of changes required to reach the malignant state, which usually requires several decades to occur, can occur over a shorter period.

Finally, understanding the development of cancer as a multistep process also explains the lag time that often separates exposure to a cancer-causing agent and the development of cancer. This explains, for example, the observation that severe sunburns in children can lead to the development of skin cancer decades later in adulthood. It also explains the 20-to-25-year lag between the onset of widespread cigarette smoking among women after World War II and the massive increase in lung cancer that occurred among women in the 1970s.

The Human Face of Cancer

For most Americans, the real issues associated with cancer are personal. About 13.7 million Americans alive today have a history of cancer, according to the National Cancer Institute. In fact, cancer is the second leading cause of death in the United States, exceeded only by heart disease.

Who develops cancer, and what are their chances for surviving it? Scientists measure the impact of cancer in a population by looking at three elements: 1) the number of new cases per year per 100,000 people (**incidence rate**), 2) the number of deaths per 100,000 people per year (**mortality**, or **death rate**), and 3) the proportion of patients alive at some point after their initial diagnosis of cancer (**survival rate**). Data on incidence, mortality, and survival are collected from a variety of sources. For example, in the United States there are many statewide cancer registries and some regional registries based on groups of counties, many of which surround large metropolitan areas. Some of these population-based registries keep track of cancer incidence in their geographic areas only; others also collect follow-up information to calculate survival rates.

In 1973, the National Cancer Institute began the Surveillance, Epidemiology, and End Results Program (SEER) to estimate cancer incidence and patient survival in the United States. SEER collects cancer incidence data in 17 geographic areas containing a combined population of about 28 percent of the entire U.S. population. Data from SEER are used to track cancer incidence in the United States by primary cancer site, race, sex, age, and year of diagnosis. For example, **Figure 5** shows SEER data for the age-adjusted cancer-incidence rates for the 10 most common sites for Caucasian and African American males and females for 2000–2004.

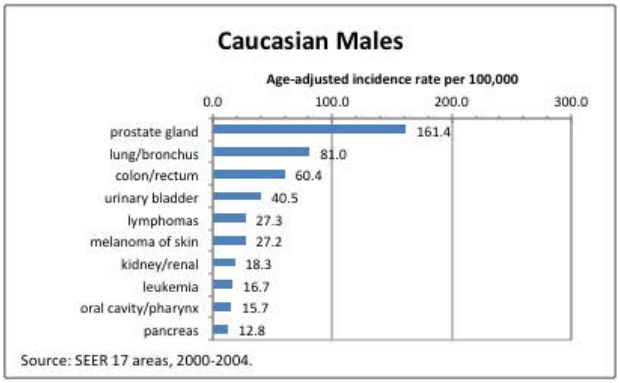
Cancer among children is relatively rare. SEER data from 2005–2009 showed an incidence of only 15.4 cases per year per 100,000 children under age 15. Nevertheless, after accidents, cancer is the second leading cause of childhood death in the United States. Leukemias (5.0 per 100,000 per year) and cancer of the brain and other nervous system organs (3.2 per 100,000 per year) account for more than one-half of the cancers among children.

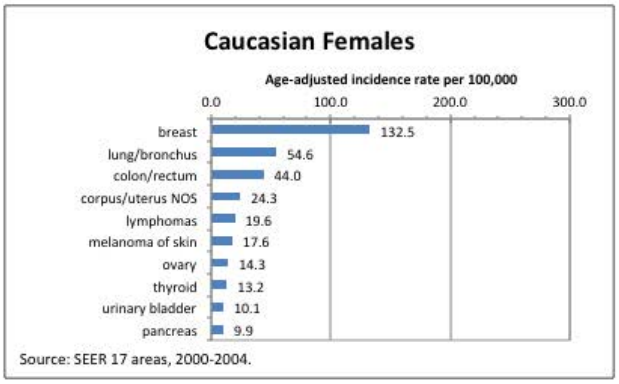
Everyone is at some risk of developing cancer. Cancer researchers use the term **lifetime risk** to indicate the probability that a person will develop cancer over the course of a lifetime. In the United States today, men have a 45 percent lifetime risk of developing invasive cancer, while women have a 38 percent risk.

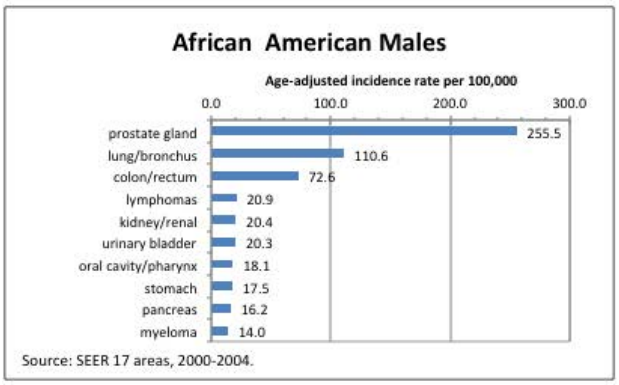
For a specific individual, however, the risk of developing a particular type of cancer may be quite different from someone else's lifetime risk of developing the same type of cancer. **Relative risk** compares the risk of developing cancer between people in one group, such as those with a certain exposure or characteristic, and people in another group, such as those who do not have this exposure or characteristic. For example, according to the American Cancer Society, a person who smokes has a 10-to-20-fold higher risk of developing lung cancer than a person who does not smoke.

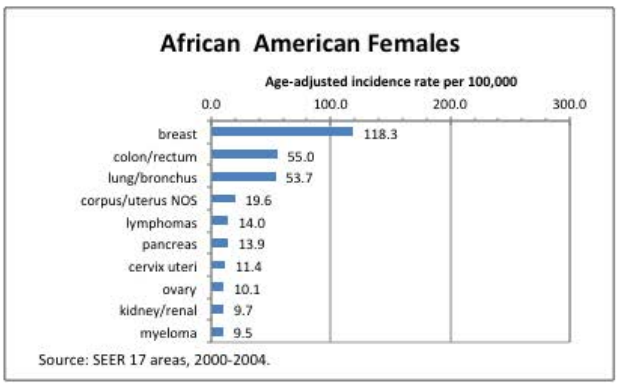
Scientists rely heavily on epidemiology to help them identify factors associated with the development of cancer. Epidemiologists look for factors that are common to cancer patients' histories and lives and evaluate these factors in the light of the current understanding of the disease. Through other kinds of studies, researchers may assemble evidence that a particular factor "causes" cancer, that is, that exposure to the factor increases the probability that cancer will develop. Although it is not

Figure 5. *Age-adjusted cancer incidence rates, 2000–2004.*









possible to predict what will happen to any one individual who has a known risk factor, it can help people make behavior choices that reduce their risk of cancer and increase the probability that if cancer develops, it will be detected early (for example, by getting regular checkups and recommended cancer screening tests).

As noted above, hereditary factors can also contribute to the development of cancer. Some people are born with mutations that promote the unrestrained growth of certain cells or the occurrence of more mutations. These mutations, such as the mutation identified in the 1980s that causes retinoblastoma, confer a high relative risk of cancer. Such mutations are rare in the population, however, accounting for the development of about 5 percent of the cases of fatal cancer.

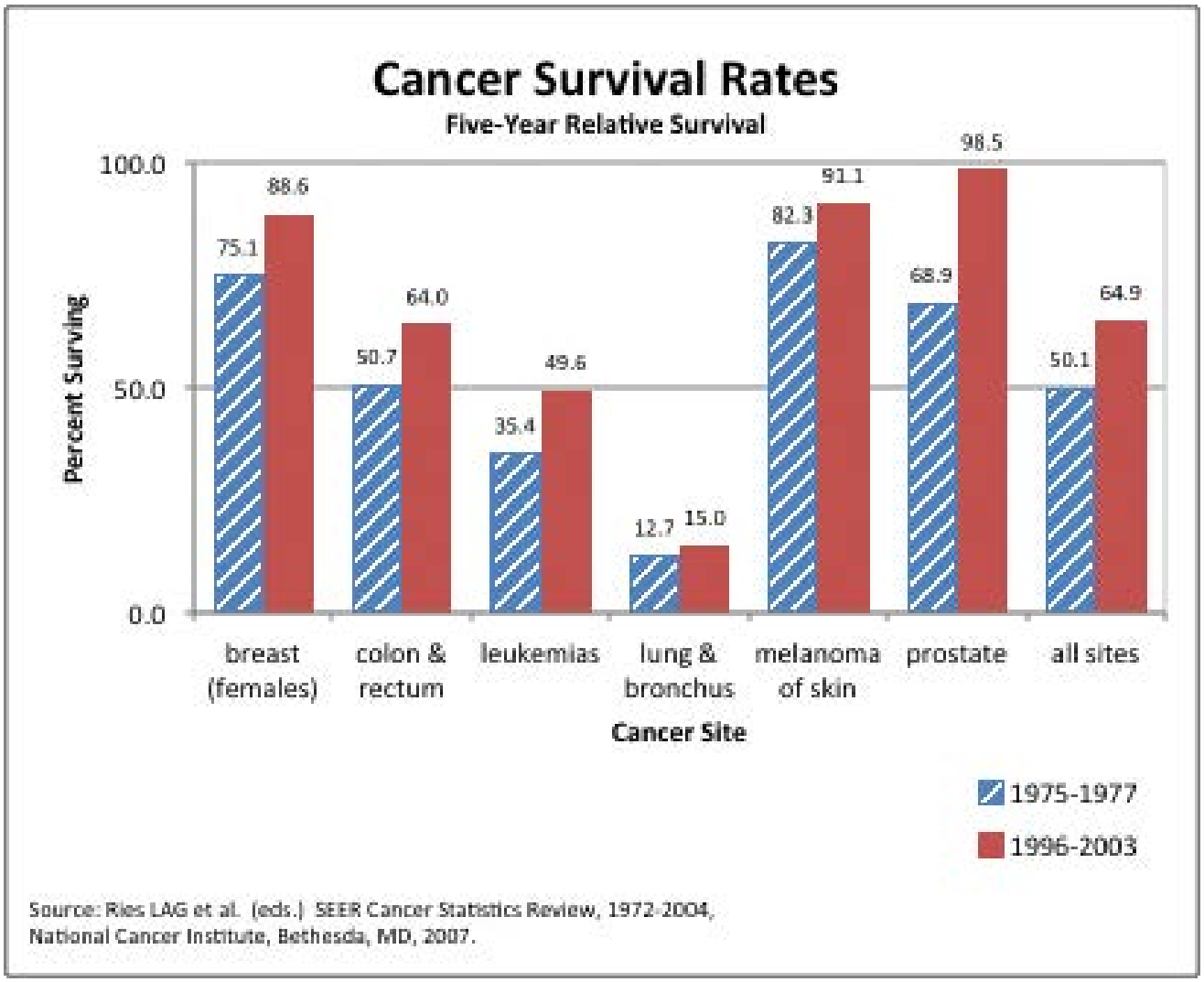
Hereditary factors also contribute to the development of cancer by dictating a person's general physiological traits. For example, a person with fair skin is more susceptible to the development of skin cancer than a person with a darker complexion. Likewise, a person whose body metabolizes and eliminates a particular carcinogen relatively inefficiently is more likely to develop types of cancer associated with that carcinogen than a person who has genes that encode more-efficient forms of the proteins involved in that particular metabolic process. These inherited characteristics do not directly promote the development of cancer; each person, susceptible or not, must still be exposed to the related environmental carcinogen for cancer to develop.

According to the American Cancer Society, about one-third of cancer deaths in the United States are due to smoking and another one-third are due to overweight/obesity, lack of physical activity, and poor nutrition. Comparing populations around the world with very different cancer patterns has led epidemiologists to suggest that perhaps only about 25 percent of all cancers are "hard wired"—that is, would develop anyway, even in a world free of external influences. These cancers would occur simply because of the random occurrence of unrepaired genetic mistakes.

Although cancer continues to be a significant health issue in the United States, a recent report from the American Cancer Society (ACS), National Cancer Institute (NCI), and Centers for Disease Control and Prevention (CDC) indicates that health officials are making progress in controlling the disease. According to a recent Annual Report to the Nation, the incidence rate for all cancers increased from 1975 through 1992, stabilized for several years, and then decreased 0.7 percent a year from 1999 through 2008. After many years of increasing cancer death rates, a turnaround occurred in 1993; there has been an acceleration in the annual decline, with decreases of 1.6 percent per year during the period of 2004–2008.

The five-year relative survival rate (that is, survival among cancer patients compared with that of cancer-free individuals of the same age, race, and sex) for all cancer sites combined also continues to increase, from 50 percent in 1975–1977 to 65 percent in 1996–2003 (**Figure 6**). By 2002-2008, this value had increased further, to 68 percent. In some cases—for example, among children age 15 and younger—survival rates have increased dramatically.

Figure 6. *Five-year relative survival rates for selected cancer sites, all races.*



New Hope for Treating Cancer

What explanation can we offer for the increase in five-year survival rates? The increase reflects both progress in diagnosing certain cancers at earlier stages and improvements in treatment.

Improvements in diagnosis have resulted from a variety of new imaging techniques as well as blood and other tests. Today, the traditional workhorses of cancer treatment—surgery, radiation, and chemotherapy along with targeted and hormone therapies—are being used in ways that are increasingly specific to the type of cancer involved.

How can we improve diagnosis and treatment? What will the future bring? Hellman and Vokes, in a 1996 article in *Scientific American*, noted that war often serves as a metaphor for cancer research. In 1971, two days before Christmas, President Richard M. Nixon signed the National Cancer Act, committing the United States to a "war" on cancer. NCI no longer uses the metaphor of a "war" on cancer. Harold Varmus, director of NCI, has pointed out that a war implies a single enemy, whereas cancer is multiple diseases. Also, cancer results when genetic control of development goes awry and does not represent an external enemy. Although the analogy is not perfect, Hellman and Vokes suggest that it can help us understand our current position with respect to cancer prevention, detection, and treatment. Looking at the "map" of cancer research after more than 40 years of "war," we can see that we have made some advances. But these successes do not reveal the tremendous developments that lie ahead of us by virtue of the new, strategic position we have achieved. In fact, most scientists expect that new insights into the molecular basis of cancer are giving rise to a whole generation of exciting new techniques, not only for detecting and treating cancer but also for preventing it.

A key area of interest lies in learning how to exploit the molecular abnormalities of cancer cells to bring about their destruction. For example, understanding the role of oncogenes in the development of cancer suggests new targets for anticancer therapies.

A better understanding of the role of tumor-suppressor genes in preventing runaway cell division may also help scientists develop new therapies directed at these genes. For example, various studies have shown that introducing a normal tumor-suppressor gene into a cell can help restore the cell to normalcy. Similarly, a therapy capable of restoring a cell's capacity for apoptosis would improve significantly the effectiveness of current cancer treatments. In fact, several targeted therapies that induce apoptosis have already been approved. Even telomerase represents an important potential target for scientists looking for new and more powerful treatments for cancer. If telomerase could be blocked in cancer cells, their telomeres would continue to shorten with each division until their own proliferation pushed them into a genetic crisis and death.

Research on molecular abnormalities in cancer cells has led to the development of a number of drugs that have come onto the market in recent years that specifically target abnormal receptor proteins and proteins within the cytoplasm that transmit stimulatory signals. Continued research is under way to identify additional promising molecular targets, and to test the effectiveness of new targeted therapies.

Recently developed laboratory techniques give researchers the increased ability to detect single-nucleotide polymorphisms (SNPs) in an individual's genome. Genetic material from different sample populations can be analyzed using **genome-wide association studies** (GWAS) to determine whether particular variations in genomic sequences are associated with specific diseases. The hope is that therapies can be developed to target the particular gene or its product where the cancer-associated variation occurs. This type of information is an example of a more integrative approach to cancer research, in which basic science, population studies, informatics, and clinical investigations all intersect in an effort to develop more-precise treatment options.

In another bold research move—fewer than three years after the completion of the Human Genome Project (HGP) in 2003—the National Institutes of Health launched the pilot stage of an effort to create a comprehensive catalog of the genomic changes involved in cancer: The Cancer Genome Atlas (TCGA)(NCI and NHGRI, 2012). The HGP laid a solid foundation for TCGA by creating a standardized reference sequence of the 3 billion DNA base pairs in the genome of normal human tissues. TCGA—now focused on 20 cancers—will characterize a number of genomic alterations as well as the DNA sequences of specific genes and other regions of DNA from tumor tissues and compare them with normal tissue to identify the major genetic changes that drive cancer development.

The revolutionary advances in our knowledge of the molecular and cellular biology of cancer in recent decades has raised the resulting challenge to "translate" advances in basic scientific knowledge into advances in the clinic as rapidly and practically as possible. The idea of using translational research teams—multidisciplinary groups of investigators who work together to move an idea from "bench to bedside"—to achieve this goal has been gaining momentum.

One area of research that has proven particularly amenable to the translational approach is applying the knowledge of different gene-expression patterns within a specific cancer type to customize treatment for specific patients, with the ultimate goal of "personalized medicine"—treatment selected to match the unique molecular characteristics of each patient's tumor. Several breast cancer signatures have been developed to predict clinical outcomes and are being tested in trials known as TAILORx and MINDACT to see whether they are able to identify the most appropriate and effective treatments for patients (NCI, 2012a).

Molecular fingerprinting is also allowing researchers to develop new treatments specifically targeted at molecular subtypes of different cancers. Often, tumors that are indistinguishable by traditional criteria nevertheless respond differently to the same treatment. Research indicates that these different outcomes are sometimes related to the presence or absence of particular gene products. Such molecular characteristics are beginning to be used to identify patients who would benefit more from one type of treatment than another.

Efforts are also being made to streamline the often lengthy and expensive drug development process for therapeutic agents against cancer and other life-threatening illnesses. Today, 9 out of 10 compounds developed in the laboratory fail in human studies. To help jump-start the earliest phase of clinical investigations, in 2006, the U.S. Food and Drug Administration—in close consultation with the National Cancer Institute—issued new guidance documents for researchers (NCI, 2006). These documents address major barriers in the early human testing of new interventions. For example, the guidance allows scientists to test very small doses of new agents before undertaking full-scale clinical trials and to evaluate new investigational agents in exploratory studies in humans before demonstrating their manufacturability.

As important as developing new treatments is, another important goal of cancer research is to push back the detection and diagnosis of cancer to its earliest stages of development. Scientists can now envision a day when medical intervention for cancer will become focused on identifying relevant incipient disease and preventing its progression to overt disease, rather than on treating the cancer after it is well established.

Cancer and Society

But what does all this information mean for society? The financial costs of cancer loom large, not only for individual patients and their families but also for the general public and society. NCI estimated the overall annual costs of cancer in the United States at about $267 billion in 2010. This cost includes about $124.6 billion for direct medical costs and $142.4 billion for lost productivity due to premature death (NCI, 2011; Bradley et al., 2008). Treatment costs for the four

most common cancers (breast, lung, colorectal, and prostate) were almost one-half (44 percent) of the direct medical costs for all cancers (NCI, 2011).

Although early detection and successful treatment can reduce cancer deaths, preventing cancer in the first place would be most efficient. The American Cancer Society reports that "cancers that can be prevented or detected earlier by screening account for at least half of all new cancer cases" (ACS, 2011).

The persistence of unhealthy habits among Americans is widespread. Part of the reason may be that the only data we have about factors related to cancer are drawn from whole populations. These data cannot tell us who will develop cancer. Nor can they tell us whether healthy choices prevented its appearance in a particular individual.

Unhealthy habits may also persist because of the long time that elapses between the exposures that trigger the development of cancer and its actual appearance as disease. Conversely, there is a time lag between the institution of a beneficial personal habit (such as quitting smoking) or public policy (such as a ban on smoking in public spaces) and its positive impact on personal and public health.

In their article "Strategies for minimizing cancer risk," Willett, Colditz, and Mueller (1996) proposed four levels on which to focus cancer prevention efforts. The first level is that of the individual. These authors argue that because most of the actions that can prevent cancer must be taken by individuals, dissemination of accurate information directly to the American public, together with peer support for behavioral changes, is critical.

A second level is healthcare providers, who are in a position to provide both counseling and screening to individuals under their care. Here, dissemination of accurate and timely information is also key.

Figure 7. *A history of severe sunburns in childhood is strongly linked to the development of skin cancer later in life.*

A third level of prevention is the national level, where government agencies can impose regulations that help minimize the public's exposure to known carcinogens and implement policies that improve public health. Examples include regulating industries to cease using potent carcinogens and providing community facilities for safe physical activity.

Finally, a fourth level of prevention is at the international level, where the actions of developed countries can affect the incidence of cancer worldwide. Unfortunate counter-examples of this include such countries allowing or promoting the export of tobacco products and moving hazardous manufacturing processes to developing countries, where they may not be regulated.

How do we think about devising and implementing measures to improve personal and public health in a pluralist society? One way to address this question is by attending to the ethical and public policy issues raised by our understanding and treatment of cancer.

Ethics is the study of good and bad, right and wrong. It has to do with the actions and character of individuals, families, communities, institutions, and societies. During the past 2,500 years, Western philosophy has developed a variety of powerful methods and a reliable set of concepts and technical terms for studying and talking about the ethical life. Generally speaking, we apply the terms "right" and "good" to actions and qualities that foster the interests of individuals, families, communities, institutions, and society.

Here, an "interest" refers to a participant's share in a situation. The terms "wrong" or "bad" apply to actions and qualities that impair interests. Often there are competing, well-reasoned answers to questions about what is right and wrong and good and bad about an individual's or a group's conduct or actions.

Ethical considerations are complex and multifaceted, and they raise many questions. In the United States, for example, we value protecting individuals from preventable harms. We support restrictions on who can purchase cigarettes and where smoking can occur. We inform pregnant women of the risks of drinking and smoking. However, we also value individual freedom and autonomy. We do not ban cigarettes outright; instead, we allow individuals over 18 years of age to take personal risks and be exposed to the related consequences. We permit pregnant women to buy and use liquor and cigarettes.

The inevitability of ethical tradeoffs is not simply an issue in the United States. When considering differing health-policy issues between and among countries, one cannot avoid encountering a diverse array of ethical considerations. Developing countries, whose health standards often differ from those in the United States, provide different cultural approaches to cancer and different standards for marketing and using tobacco and other known carcinogens. These different approaches raise a variety of ethical questions.

For example, is there any legal and ethical way for people in the United States to prevent the widespread use of tobacco in other countries, a practice that contributes to the rise of lung cancer worldwide? Is there any legal and ethical way to govern other choices of individuals (for example, poor diet and lack of exercise) that may contribute to cancer?

Typically, answers to such questions all involve an appeal to values. A *value* is something that has significance or worth in a given situation. One of the exciting aspects of any discussion of ethics in a pluralistic society is the variation in how the individuals involved assign value to things, people, and states of affairs. Examples of values that students may appeal to in discussions of ethical issues include autonomy, freedom, privacy, sanctity of life, protecting another from harm, promoting another's good, justice, fairness, relationships, scientific knowledge, and technological progress.

Acknowledging the complex, multifaceted nature of ethical discussions is not to suggest that "anything goes." Experts generally agree on the following features of ethics. First, ethics is a process of rational inquiry. It involves posing clearly formulated questions and seeking well-reasoned answers to those questions. Well-reasoned answers to ethical questions constitute *arguments*. Ethical analysis and argument, then, result from successful ethical inquiry.

Second, ethics requires a solid foundation of information and rigorous interpretation of that information. For example, one must have a solid understanding of cancer to discuss the ethics of requiring protective covering to be worn to prevent skin cancer. Ethics is not strictly a theoretical discipline but is concerned in vital ways with practical matters.

Third, because tradeoffs among interests are complex, constantly changing, and sometimes uncertain, there are often competing, well-reasoned answers to questions about what is right and wrong and good and bad. This is especially true in a pluralistic society.

Public policy is a set of guidelines or rules that results from the actions or lack of actions of government entities. Government entities act by making laws. In the United States, laws can be made by each of the three branches of government: by legislatures (statutory law), by courts (case law), and by regulatory agencies (regulatory law).

Regulatory laws are written by the executive branch of the government, under authorization by the legislative branch. All three types of law are pertinent to how we respond to cancer. When laws exist to regulate behavior, public policy is called *de jure* public policy.

When deciding whether to make public policy, one should consider at least the following five points:

- costs of implementing particular policies (including financial, social, and personal costs);
- urgency of implementing a new policy;
- how effective a particular policy is likely to be;
- whether appropriate means exist to implement the policy; and
- social, cultural, and political factors.

For example, many argue that there is overwhelming evidence to support a public policy of increased restrictions on access to and use of cigarettes. Cigarette smoking is linked to 85 to 90 percent of lung cancer cases, and it leads to chronic lung disease and heart disease. For 2012, 226,160 new cases of lung cancer were predicted, as were 160,340 deaths due to lung cancer, lung disease, and heart disease (ACS, 2012). Public policy prohibitions on cigarette use and access may be seen to satisfy four of the five considerations: 1) the cost of the policy would probably be minimal because cigarette access and use restrictions are already in place, 2) the urgency of the situation is serious given the large number of deaths and severe illnesses, 3) prohibiting purchases by minors and raising prices (through taxation) are seen as effective, and 4) means are already in place for additional restrictions. The challenges in this era of high economic interest in cigarette production are the social, cultural, and political considerations (5).

Figure 8. *Where do we spend our money? A consequence of allowing unhealthy habits, such as smoking, is that public funds may be spent on cancer treatments instead of on other societal benefits, such as improved school facilities.*

It is important to recognize that sometimes the best public policy is *not* to enact a law in response to a controversy but rather to allow individuals, families, communities, and societies to act in the manner they choose. Clearly, de jure public policy can only go so far in regulating people's behaviors. De jure public policy in the United States offers no match for the addictive power of nicotine and the marketing clout of the tobacco industry. In addition, any decline in cigarette use brought about by de jure public policy in the United States has been more than offset in recent years by a rapid increase of cigarette consumption elsewhere in the world.

When no laws exist to regulate behavior, public policy is called *de facto* (actual) public policy. With regard to lung cancer prevention programs, many think that other approaches are needed: improved general education and cultivation of an antismoking ethos. In any discussion of society's response to a social problem, it is important to think not just about laws, but about other ways to address the problem.

Science plays an important role in helping individuals make choices about enhancing personal and public welfare. Science provides evidence that can be used to support ways of understanding and treating human disease, illness, deformity, and dysfunction. But the relationships between scientific information and human choices, and between choices and behaviors, are not linear. Human choice allows individuals to choose against sound knowledge, and choice does not necessarily lead to particular actions.

Nevertheless, it is increasingly difficult for most of us to deny the claims of science. We are continually presented with great amounts of relevant scientific and medical knowledge. We are fortunate to have available a large amount of convincing data about the development, nature, and treatment of particular cancers.

As a consequence, we might be encouraged to think about the relationships among knowledge, choice, behavior, and human welfare in the following ways:

knowledge (what is and is not known) + choice = power

power + behavior = enhanced human welfare (that is, personal and public health)

One of the goals of this module is to encourage students to think in terms of these relationships, now and as they grow older.