Cancer – A Disease Caused by Gene Alterations

Cancer is a disease of uncontrolled and invasive cell reproduction. Current estimates are that one-third of the children born today will get some form of cancer in their lifetime. Lung cancer is still a major killer, and the cause of most lung cancers is straightforward: smoking. The most common cancers are breast, (an assortment of cancers), prostate, lung and colon cancers. One in eight will get breast cancer. Almost any male who lives long enough will have prostate cancer.

Substances that cause DNA alterations that lead to cancer are carcinogens and exposure to a carcinogen is a first step in at least 80% of cancers. Studying the effect of human-made and natural mutagens is a public health issue. Identifying exposure to mutations and measuring their risk of carcinogenesis is a public policy goal. The Montreal Protocol of 1987 is an international agreement that bans all chlorofluorocarbons and related substances that promote upper atmosphere ozone depletion. Ozone holes permit increased UV radiation and lead to increased skin cancers, among other impacts. Many cities have banned smoking in public places as a result of continued research linking second-hand smoke to mutagenesis in those exposed.
Preventing exposure to potential carcinogens is important but no one really knows why any one person gets cancer when others exposed to the same environment do not. In addition to atmospheric exposure to potential mutagens, substances in foods may be cancer causing, cancer promoting or, conversely cancer preventing.

A cancer cell and its cell line typically undergo several mutations in the development of cancer. Some of us may have genes more susceptible to mutation, and about 10% of cancers are related to the inheritance of mutated alleles for genes that control cell division. Around 300 genes have been identified so far in humans that are found in tumors.

Cancer is a gene disorder that occurs in somatic tissues. Cancers result when the genes responsible for coding the proteins that regulate cell division mutate. Cancer cells do not follow normal cell cycle checkpoint signals and damaged genes no longer control cell division and cell proliferation.

Cancer cells may have abnormal plasma membranes, cytoplasm and metabolic processes as well as abnormal numbers of chromosomes, typically with many translocations. Cancer cells divide rapidly and ignore the overcrowding inhibition signals for density and anchorage dependency. They form masses of cells called tumors. Once cell controls are not in effect, rapidly dividing cancer cells lose their normal positioning and adhesion properties.

Tumors can be **benign** or **malignant**. Benign tumor cells resemble cells in the tissues in which they are found, grow slowly and do not spread to other areas of the body. None-the-less, they often need to be removed before they cause damage. Malignant tumor cells do not resemble the tissue in which they are formed and can rapidly grow and spread becoming **invasive**. The alteration of cancer cell surfaces promotes **metastasis** and migration to other areas of the body, particularly through the lymph system. Migrating cells can attach to new tissues and form more tumors.
Given adequate nutrients in culture media, many cancer cells can divide indefinitely. The HeLa cell line (cells from Henrietta Lacks) has been cultured for about seventy years, indicating that telomerase is active in cancer cell lines. Once a cell line becomes cancerous, cell division can rarely be stopped, and will continue until the individual in whom the cancer cells reside dies, unless the cancer cells can be successfully destroyed or excised surgically.

There are many different types of cancers. The categories or types of cancers are derived from their originating tissue. For example:

- Sarcomas are cancers of connective tissue, including bone and muscle tissue (which isn’t really connective tissue)
- Lymphomas are cancers of the lymph system
- Carcinomas and melanomas originate in epithelial tissue
- Adenomas develop from glandular tissues, primarily epithelial glands

**Cancer Development**

The development of cancer is a multistep process that includes:

- Exposure to a carcinogen from the environment by ingestion, inhalation, etc., naturally or via contamination
- Entry of the carcinogen into a cell
- Initiation of cancer via sufficient (usually multiple mutations) DNA changes, in cell division control genes
- Promotion and enhancement of cancer via cell transformation of a normal cell into a cancer cell
- Tumor formation and uncontrolled cell growth
Identifying Carcinogens
Because the onset of cancer is usually an accumulation of mutations rather than a single alteration, research today focuses on what causes the mutations that result in the loss of genes that regulate cell division.

Ionizing and UV radiation and combustion products of tobacco are three common carcinogens. Asbestos and many heavy metals in particulate form are carcinogens, as are any number of other chemicals found in our environment. Steroids in higher than normal concentrations are carcinogenic, and a high fat, low fiber diets may be cancer promoting, or perhaps foods that are rich in fiber and low in fat have some other substances that promote health that are missing in the high fat, low fiber diet. Recent studies indicate that low levels of vitamin D may be a factor in some cancers. Some viruses also promote some cancers.

Chemical Carcinogens
The evidences for chemical carcinogens is compelling, both from laboratory study of controlled chemical exposure and population studies that correlate chemicals in the environment and/or workplace with increased rates of cancer.

Dr. John Hill first proposed that chemicals promote cancer in the 1700's. He postulated that chemicals in tobacco caused the nose tumors common in those who used snuff. It was also noted during that time period that chimney sweeps were more likely to get tumors and a probable cause of those tumors was the constant exposure to soot. That coal tars induce cancer in rabbits was shown by Yamigawa in 1915. Cancers caused by cigarette tars was documented in 1949.

Over the past half-century the list of known chemical carcinogens has grown.
Cancer and Viruses

There are human cancer-causing viruses, as well as viruses that cause cancers in plants and other animals. Peyton Rous identified the first known cancer-causing virus in 1911. This virus, the Rous avian sarcoma virus, or RSV, was isolated from cultured chicken sarcoma (bone and connective) tissue. The isolated virus was then used to infect normal chicken connective tissue by transfection (DNA from one cell introduced into another cell). Research demonstrated that RSV that did not cause cancer was missing a particular gene, named src (sarcoma causing), and RSV that caused cancer had a particular form of the src gene.

Subsequently, Harold Varmus, Michael Bishop and Peter Vogt discovered that normal chicken cells have a normal src gene, and that chickens most likely obtained an altered form of src from RSV that inserted the cancer-inducing allele into the chicken DNA during the viral replication process.

Human HPV is linked to cervical cancer, some liver cancer is related to the Hepatitis B virus and Burkitt's lymphoma is related to the Epstein-Barr virus. One form of leukemia is linked to a virus. Cat leukemia is also caused by a virus.
Cancer Genes: Proto-oncogenes, Oncogenes and Tumor Suppressor Genes

Oncogenes – the Cancer Promoting Genes

A gene that has the potential to induce cancer is called an **oncogene**. Oncogenes are positive regulators in cancer because they enhance cell division by being overactive or over productive, hence stimulating cell division. Rous discovered oncogenes when he observed the transfection of normal chickens when infected with RSV. RSV caused a normal cell division regulatory gene (src) to become non-functional. The virus carried a gene that coded for a receptor enzyme for a signal molecule in the tyrosine kinase transduction pathway that functions in the cell cycle, but since the gene was within the virus, it was not under the normal chicken gene regulation controls. The virus could direct transcription and translation of the enzyme, so the signal transduction pathway could be "permanently" active despite the chicken's own gene controls. Since that time, many oncogenes have been identified.

**Proto-oncogenes**

Oncogenes start out as present in our cells that code for proteins that regulate normal cell growth and division by determining the appropriate rate of cell division. Genes that regulate normal rates of cell division are called **proto-oncogenes** because mutations in proto-oncogenes result in the loss of those regulating controls. Many proto-oncogene gene products are growth factors that activate cell growth signal transduction pathways. Increase in the production of growth factor receptors also serves to promote cancer. When a proto-oncogene becomes an oncogene the result is the over-production of the gene's product or, in many cases, an increased activity of growth factors that activate cell division.

**Increase in Growth Factor Receptors in Breast Cancer Cell**

"Something" causes a proto-oncogene to mutate into an active oncogene. There are many suspect ways in which proto-oncogenes can be changed into oncogenes:

- Translocation of the gene to a new area that now has a more receptive promoter region. Cancer cells often have broken chromosomes with translocated fragments.
- Gene amplification so that many more copies of the gene can be transcribed.
• Point mutation in a controller or promoter region that results in an actively coded gene, or in the codable region that enhances the product function.
• Viruses can be oncogene vectors if the virus inserts a mutated form of the proto-oncogene along with a viral promoter that can be transcribed.

An oncogene promotes cancer when it is over-produced or overactive so cell division controls are always "on". One of the first oncogenes studied, the transcription factor myc, was present in 10 times the normal amount in a form of leukemia. The myc gene promotes the production of cyclins and the cyclin-dependent kinases needed for cell division. Normal suppression the myc gene regulates the level of cyclin in the cell; when myc is mutated, resulting in the oncogene, cyclin production is over-stimulated and cells can rapidly divide.

The Ras G-protein is a G-protein that activates a tyrosine-kinase pathway resulting in the synthesis of a protein that stimulates the cell cycle; hence the Ras G-protein can control the rate of cell division. If the ras proto-oncogene mutates to become "hyperactive" Ras oncogene, cell division occurs at an uncontrolled rate. The ras oncogene mutation was first identified in cancer cells.

Oncogenes work with other carcinogens. Oncogenes, by themselves, cannot produce cancers. Because an oncogene acts in the absence of its normal control, however, oncogenes can be inherited as expressible "dominant" alleles.
Tumor Suppressor Genes
Tumor suppressor genes code for proteins that function to monitor DNA for damage and to signal its repair, or, when damage cannot be repaired, prevent cell division from taking place and/or to signal destruction of the cell by apoptosis. Tumor suppressor genes are negative regulators in normal cells.

The genes that code for the cell division checkpoint binding proteins such as RB are also tumor suppressor genes. Hence, normal tumor suppressor genes minimize the chances of cancer-causing mutations. Our tumor suppressor genes are the reason that oncogenes, by themselves, do not cause cancer. In addition to activating oncogenes, we need to inactivate tumor-suppressing genes to trigger the uncontrolled growth associated with cancer.

When mutations occur in the tumor-suppressing genes that code for factors that activate mutation-"catching" proteins, the normal cell division inhibitions are affected, and cells with damaging mutations proliferate. In that sense, mutated tumor-suppressor genes also become oncogenes.

Viruses, such as the HPV virus can block function of tumor suppressor proteins. HPV blocks RB so RB cannot regulate the cell cycle.

\( p53, \ p16, \ p21 \) and \( Rb \) are proteins that monitor damaged DNA at cell division checkpoints. \( p53- \) and \( Rb \)-related transcription factors have mutations in their genes in about 40 – 50% of all cancers. Other proteins involved in the kinase relay pathways also show mutations in many cancers.

\( p53 \) is a transcription factor that initiates transcription of a protein called p21. p21 blocks cyclin from binding to the cdk if there is damage to a cell, keeping the cell in the \( G_1 \) phase to provide time for DNA repair.

p53 can also promote synthesis of transcription factors that initiate transcription of DNA repair enzymes.

When damage cannot be repaired, p53 activates genes for apoptosis to prevent damaged cells from continuing to divide.
The **p16, p21** and **Rb** tumor-suppressor genes are similar to p53, working collaboratively to block cell growth in G₁ by preventing transcription factors needed for cell division from working.

Rb is a block that keeps cells in G₁. Rb normally gets removed from its blocking position when the cyclin-cdk complex builds to sufficient quantity.

p16 and p21 can block the cyclin-dependent kinase from binding to cyclins keeping cells in G₁ when there is damage to a cell.

(E2F is transcription factor that turns genes on for cell division.)
Inactivating Tumor-Suppressor Genes

Normal tumor-suppressor genes can be inactivated by mutation. Mutations in genes that normally suppress cell division can result in abnormal growth, since the gene can no longer suppress growth activity. Thus a tumor-suppressor gene is considered a proto-oncogene in the sense that when mutated, cancer can result. Most mutations occur in somatic cells, and are not inherited.

One area of cancer research today focuses on causes of tumor-suppressor gene mutations, which result in the loss of function. There are three ways identified:

- Mutation in the promoter region or an early point mutation that codes for the stop codon both prevent synthesis of the gene product.
- Chromosome loss (by translocation or deletions) means the gene can't be found to transcribe.
- Abnormal DNA methylation is found in some cancer cell tumor-suppressor genes, particularly near the promoter regions.

In contrast to cell division activating proto-oncogenes, both alleles of a tumor suppressor gene must be inactivated to promote cancer, because an unaffected allele can still code for the monitor protein. This is known as the "two-hit" cancer hypothesis, first proposed when a tumor-suppressor gene, Rb (for retinal blastoma), caused a retinal cancer when both alleles were mutated. Individuals who inherited one mutated allele often developed retinal cancer at a fairly early age. (The retina has over 1 million cells, so mutations are more likely at an earlier age than in some other tissues.) Those who did not inherit one mutated allele, have a later onset.

Two tumor suppressing genes involved in breast cancer were identified in the mid-1990's: BRCA1 and BRCA2. Since then, over 600 different mutations: deletions, insertions and substitutions have been identified in BRCA1. A mutation in either of these two genes increases the risk of breast, ovarian and prostate cancers.
In all cases, mutations in cell division control genes result in increased cell division. The mutation could be in a gene that normally is moderated so that gene becomes always "on". Conversely, it might be a gene that monitors the checkpoints for damage that is no longer being coded, so the checkpoint no longer "checks". Generally both happen in cancers.

Comparing the Effects of Mutation on Proto-Oncogenes and Tumor Suppressor Genes

**Oncogene Mutations and Effects**

<table>
<thead>
<tr>
<th>Normal G1 to S arrest:</th>
<th>Mutated growth factor receptor gene:</th>
<th>Mutated cyclin gene:</th>
</tr>
</thead>
<tbody>
<tr>
<td>growth factors receptor</td>
<td>growth factors receptor always &quot;on&quot;</td>
<td>growth factors receptor always &quot;on&quot;</td>
</tr>
<tr>
<td>cyclin synthesis</td>
<td>cyclin synthesis</td>
<td>cyclin synthesis</td>
</tr>
<tr>
<td>Cdk</td>
<td>Cdk</td>
<td>Cdk</td>
</tr>
<tr>
<td>phosphorylates Rb</td>
<td>phosphorylates Rb</td>
<td>phosphorylates Rb</td>
</tr>
<tr>
<td>Rb → P</td>
<td>Rb → P</td>
<td>Rb → P</td>
</tr>
<tr>
<td>DNA replication</td>
<td>uncontrolled DNA replication</td>
<td>uncontrolled DNA replication</td>
</tr>
</tbody>
</table>

**Mutated Rb gene:**

- DNA damage prevents G1 → S
- DNA damage + receptor
- cyclin synthesis
- Cdk
- mutated Rb does not require phosphorylation
- Rb
- uncontrolled DNA replication
- no DNA replication

**DNA damage prevents G1 → S:**

- DNA damage
- mutated p53 cannot block Rb phosphorylation
- cyclin synthesis
- Cdk
- phosphorylates Rb
- Rb → P
- replication of damaged DNA

**Tumor Suppressor Mutations and Effects**

**Cancer and Apoptosis**

As mentioned, apoptosis is important in cells in which there has been genetic damage. Cell division would perpetuate the damage possibly leading to abnormal growth and cancers.

Genes activated by the protein, p53, function in apoptosis. If p53 detects DNA damage, it activates genes that code for enzymes to either repair the damage prior to cell division, or, if repair is not possible, p53 activates apoptosis genes.

If the p53 gene is defective, DNA damage may not be detected and damaged cells can continue to divide, which can lead to cancers.
Apoptosis genes have opposing oncogenes (cancer-promoting genes) that repress the activity of the apoptosis gene. For example, the \textit{bax gene} is an apoptosis gene in humans. The \textit{bax} gene must be transcribed to synthesize the bax protein needed for apoptosis. However, \textit{bcl-2}, an oncogene, can prevent transcription of the bax enzyme leading to growth of defective cells (and subsequently cancer).

With defective DNA, apoptosis is desirable – we are attempting to destroy a damaged cell that otherwise could divide without restraint to form cancer. In these cases, \textit{bcl-2} blockage of \textit{bax} is not a good thing.

\textbf{Telomerase and Cancer}

Normal cells have a tumor-suppressing gene that blocks the synthesis of telomerase. A normal cell can divide about 20 – 30 times before it reaches the end of its telomeres, and dies. A mutation in the gene that represses synthesis of telomerase permits cells to regenerate telomeres, so that normal telomere-limiting control is absent. Cancer cells that have active telomerase can divide "forever".

Being able to synthesize telomerase doesn't cause cancer – but it permits cells that have additional mutations that affect the cell cycle to divide indefinitely so that the tumors can grow.

\textbf{Cancer and Accumulated Mutations}

We know accumulated mutations lead to cancer development. For example, several mutations are identified in polyp cells that can become colon cancer tumors, including mutations in \textit{APC} (a gene involved in cell migration and adhesion), \textit{Ras} and \textit{p53}. Similar genes have been identified in both lung cancers.
Since it appears that most cells need multiple mutations to become malignant, age is often a factor in cancer. Studies have confirmed that mutations occur at a greater rate in cells as one ages. Exposure to a number of carcinogens during one's lifetime may be as important as the intensity of exposure. Ionizing radiation exposure is directly dose-related.

More than one-fourth of the cancer deaths in the United States each year are from lung cancer. 90% of those diagnosed with lung cancer are smokers. Combustion products in smoke, which is inhaled into the lung tissue, contain potent carcinogens, including benzo-α-pyrene. Once benzo-α-pyrene is absorbed into the epithelial cells of the lungs, a derivative mutates p53. Mutated p53 is found in 70% of all lung cancers.

**Some Current Research on Cancer Therapies**

The cancer therapies researched today relate directly to the role of gene activation in the cell cycle. Just as researchers have identified target genes (oncogenes and tumor-suppressor genes) where mutations occur, they are now working to counter the effects of those mutations throughout the multitude of steps involved in the cell cycle. The cancer therapies researched today relate directly to the role of gene activation in the cell cycle. Just as researchers have identified target genes (oncogenes and tumor-suppressor genes) where mutations occur, they are now working to counter the effects of those mutations throughout the multitude of steps involved in the cell cycle.
Targets for cancer therapies include:

- Signal receptors for growth factors in plasma membrane
- Transduction relay switch
- Amplification of signals
- Nuclear controls of $G_0$ status
- DNA integrity check proteins
- Chromosome distribution in Mitosis
- Telomerase Inhibition
- Angiogenesis

**Cancer Targets and Treatments**

**Signal Receptors**

If the cancer is one that amplifies signal reception, one therapy is to block the receptor with a competitor. For example, 20% of breast cancers overproduce a protein, called HER2, which over-stimulates a signal receptor for a growth factor. Through genetic engineering, protein antibodies have been produced that target HER2 for destruction by the immune system. These specifically targeted antibodies are called **monoclonal antibodies**.

Monoclonal antibodies have also been used successfully on some melanomas in current cancer trials. They are using cancer cells extracted from the cancer patient to stimulate antibody formation in culture. The cloned antibodies are then injected back into the patient and target the cancer cells.

**Ras Inactivation Preventing Amplification**

Overactive ras protein triggers signal transduction pathways that lead to more frequent cell division.

- Normal ras is inactive, and must be activated by an enzyme. A possible cancer treatment is repression of the enzyme that activates ras.
- Signal transduction pathways activated by ras are protein-kinase amplification pathways. Blocking the ras activated pathways can stop cancer growth by slowing the amplification pathway.

**Blocking src**

The src pathway is also a protein-kinase pathway. Since src uses complementary RNA to make copies of itself, a potential cancer treatment would be overwhelming src with **anti-sense RNA** that would bond to src but not allow replication.
The G₁ checkpoint and Rb
The tumor-suppressor Rb blocks cell division by binding to a protein called E2F during G₁. E2F promotes cell division. As mentioned, the cyclin-cdk complex phosphorylates Rb removing it from E2F so that cell division can proceed. In the absence of Rb, E2F is always active. 40% of all cancers have defective Rb. Drugs that could inhibit E2F might be a good cancer treatment.

DNA duplication
Some chemotherapeutic drugs, such as irinotecan and 5-fluorouracil, inhibit enzymes needed for DNA synthesis in the S phase of Interphase.

p53 Mutations and DNA Integrity Check
Virus therapy may prove promising for countering mutant p53. Adenoviruses contain a gene that inactivates p53 so that the host cell can be used to synthesize virus DNA. A mutant virus with no p53 inactivator gene could be used to destroy cancer cells that have mutant p53 but could not damage normal cells. (In a normal cell, p53 could not be inactivated to permit the replication of virus DNA.)

Radiation therapy damages DNA, so damaged cells are targeted for apoptosis by normal integrity checking proteins.

Mitosis Checkpoint
Chemotherapeutic drugs such as Paclitaxol (originally derived from a terpene from the western yew tree, Taxus brevifolia, and vinblastine, derived from a Madagascar periwinkle, interfere with the separation of chromosomes during mitosis. Other drugs also target the cell cycle.

Telomerase
Without telomerase cell division is limited. Re-repressing telomerase would have much promise in slowing and halting tumor growth.

Angiogenesis Inhibitors
When tumors grow, they promote formation of new blood vessels to "feed" the tumor cells, a process called angiogenesis. Blocking new blood cell formation can starve a tumor causing it to shrink. No tests have yet been done on humans.

Tumors Spreading
Some cancers metastasize. Once tumors spread, surgical removal becomes far more difficult if not impossible. Chemicals that prevent migration of cells may prove useful in preventing the metastasis of cancers.
These are but a few of the many areas targeted for research today. Even with such promising research, each cancer must be identified, the factors promoting that cancer known and appropriate mix of treatments provided. Although it might seem that great strides are being made (and they are) most of what we have just mentioned is, at best, in testing stages – not available for the public.

**Treatment Targets**

In addition to conventional cancer treatments of chemotherapy and radiation, alternative therapies are also being investigated for their potential to arrest cancer development, particularly with botanical extracts. Recalling that some of our best chemotherapy drugs are specific chemical extracts from plant sources, such research has promise. However, today, herbal supplements are not regulated, and may have dozens of unknown substances in their ingredients as well as unknown concentrations of the extract that may hold promise. In one study, the herbal extract, PHY906, in combination with irinotecan, enhanced the anti-tumor irinotecan therapy in mice colon tumors. The PHY906 alone did not arrest tumor growth.
Some Information on Oncogenes Categories
Oncogenes can be categorized by their specific action. Categories include:

- Growth factors
- Membrane and cytoplasmic growth factor receptors
- Transduction protein kinases
- Transcription factors
- G-proteins
- Nuclear proteins (cyclins, tumor suppressor or apoptosis antagonists)

Some Tumor Suppressor Genes

**p53**
- p53 is a transcription factor that positively regulates a few specific target genes and negatively regulates others in a general manner. It acts as a sensor of DNA damage. It can prevent the progression through the cell cycle and also can promote apoptosis.

**BRCA-1 and BRCA-2**
- Brca-1 and Brca-2 proteins are both involved in the cellular defense against DNA damage. They may play a role in sensing DNA damage, or they may act to facilitate DNA repair. These genes are sometimes mutant in persons with inherited forms of breast cancer.

**XPD**
- This represents several different genes whose products function in DNA repair. These genes are defective in patients with xeroderma pigmentosum.

Inhibit cell division (negative regulators):
- **Rb**: The Rb protein is a negative regulator that represses the transcription of genes required for DNA replication and cell division.
- **NF1**: The NF1 protein stimulates Ras to hydrolyze its GTP to GDP. Loss of NF1 function causes the Ras protein to be overactive, which promotes cell division.
- **p16**: A negative regulator of cyclin-dependent protein kinase.
### Some Genes Involved in Cancers

<table>
<thead>
<tr>
<th>Gene</th>
<th>Product</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONCOGENES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erb-B</td>
<td>Receptor for epidermal growth factor</td>
<td>Glioblastoma (a brain cancer); breast cancer</td>
</tr>
<tr>
<td>erb-B2</td>
<td>A growth factor receptor (gene also called neu)</td>
<td>Breast cancer; ovarian cancer; salivary gland cancer</td>
</tr>
<tr>
<td>PDGF</td>
<td>Platelet-derived growth factor</td>
<td>Glioma (a brain cancer)</td>
</tr>
<tr>
<td>RET</td>
<td>A growth factor receptor</td>
<td>Thyroid cancer</td>
</tr>
<tr>
<td><strong>Genes Encoding Cytoplasmic Relays in Intracellular Signaling Pathways</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-ras</td>
<td>Protein kinase</td>
<td>Lung cancer; colon cancer; ovarian cancer; pancreatic cancer</td>
</tr>
<tr>
<td>N-ras</td>
<td>Protein kinase</td>
<td>Leukemias</td>
</tr>
<tr>
<td><strong>Genes Encoding Transcription Factors That Activate Transcription of Growth-Promoting Genes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-myc</td>
<td>Transcription factor</td>
<td>Lung cancer; breast cancer; stomach cancer; leukemias</td>
</tr>
<tr>
<td>L-myc</td>
<td>Transcription factor</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>N-myc</td>
<td>Transcription factor</td>
<td>Neuroblastoma (a nerve cell cancer)</td>
</tr>
<tr>
<td><strong>Genes Encoding Other Kinds of Proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bcl-2</td>
<td>Protein that blocks cell suicide</td>
<td>Follicular B cell lymphoma</td>
</tr>
<tr>
<td>bcl-1</td>
<td>Cyclin D1, which stimulates the cell cycle clock (gene also called PRAD1)</td>
<td>Breast cancer; head and neck cancers</td>
</tr>
<tr>
<td>MDM2</td>
<td>Protein antagonist of p53 tumor-suppressor protein</td>
<td>Wide variety of sarcomas (connective tissue cancers)</td>
</tr>
<tr>
<td><strong>TUMOR-SUPPRESSOR GENES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>Step in a signaling pathway</td>
<td>Colon cancer; stomach cancer</td>
</tr>
<tr>
<td>DPC4</td>
<td>A relay in signaling pathway that inhibits cell division</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>NF-1</td>
<td>Inhibitor of Ras, a protein that stimulates cell division</td>
<td>Neurofibroma; myeloid leukemia</td>
</tr>
<tr>
<td>NF-2</td>
<td>Inhibitor of Ras</td>
<td>Meningioma (brain cancer); schwannoma (cancer of cells supporting peripheral nerves)</td>
</tr>
<tr>
<td><strong>Genes Encoding Nuclear Proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTS1</td>
<td>p16 protein, which slows the cell cycle clock</td>
<td>A wide range of cancers</td>
</tr>
<tr>
<td>p53</td>
<td>p53 protein, which halts cell division at the G1 checkpoint</td>
<td>A wide range of cancers</td>
</tr>
<tr>
<td>Rb</td>
<td>Rb protein, which acts as a master brake of the cell cycle</td>
<td>Retinoblastoma; breast cancer; bone cancer; bladder cancer</td>
</tr>
<tr>
<td><strong>Genes Encoding Proteins of Unknown Cellular Locations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>?</td>
<td>Breast cancer; ovarian cancer</td>
</tr>
<tr>
<td>BRCA2</td>
<td>?</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>VHL</td>
<td>?</td>
<td>Renal cell cancer</td>
</tr>
</tbody>
</table>