Intro to cancer genetics:
http://www.cancer.gov/cancerinfo/

How many somatic cells is an adult human made of?
• An adult human has somewhere around $10^{14}$ cells
• In the mature organism some cell types divide continually (such as epithelial cells and cell lining the GI tract)
• Other cell types divide rarely
• Since too few or too many cell divisions could produce chaos in a particular organ, the growth and division of each cell type is very carefully controlled
• Cancers result when single cells in the body and change their behavior relative to neighboring cells
Somatic cells exist in a “social” setting where they need to be responsive to cues from neighboring cells.

Cancer cells can be thought of as rogue cells that no longer obey the rules of the social contract.
Cancer cells differ from normal cells in the following ways (see text figure 18.16):

1. The cells mutate so that they can dodge the cellular signals that suppress growth [or that encourage suicide of genetically abnormal cells]
2. The cells acquire their own growth-signalling pathways, independent of the external signals that normal metazoan cells are dependent on
3. They develop limitless potential to proliferate: normal cells can divide only about 70 times before their telomeres (huh?) become so shortened that the chromosomes are damaged and the cell dies
4. Solid tumor cells create their own network of blood vessels (to supply the growing monster with food and oxygen)
5. Finally the most dangerous tumor cells are those that can travel to distant sites in the body (metastasis). Nine of ten cancer deaths result from metastases.
Cancers are diseases in which unremitting clonal expansion of somatic cells kills by invading, subverting and eroding normal tissues.

- A tumor develops through repeated rounds of mutation and proliferation, giving rise eventually to a clone of fully malignant cancer cells.
- Mutations that enhance proliferation increase the chance of that the next step in tumor progression will occur by increasing the size of the cell population at risk of undergoing another mutation.
Cancer results from *stochastic, somatic cell mutations* in genes that govern and regulate the diverse aspects of growth control in multicellular organisms.

Rate of cell proliferation is controlled by *growth promoting* and *growth suppressing* signal transduction pathways.

(Text figure 18.15)
Text figure 18.15

What would the effect of loss-of-function mutations in a growth inhibiting pathway be?
What would the effect of loss-of-function mutations in a growth promoting pathway be?
How then can mutations in a growth promoting pathway result in increased cellular proliferation?
<table>
<thead>
<tr>
<th>Loss-of-function</th>
<th>Gain-of-function</th>
</tr>
</thead>
<tbody>
<tr>
<td>• partial or complete loss of gene function</td>
<td>• increased level of wild-type gene product</td>
</tr>
<tr>
<td>• common -- why?</td>
<td>• increased level of wild-type gene product</td>
</tr>
<tr>
<td>• typically recessive</td>
<td>• altered function of protein: <em>unregulated activity of protein</em></td>
</tr>
<tr>
<td>• dominant if gene is <em>haploinsufficient</em></td>
<td>• altered temporal or spatial expression of gene product</td>
</tr>
<tr>
<td></td>
<td>• dominant</td>
</tr>
</tbody>
</table>
Scientific American Sept. 1996
Most cancers result from the accumulation of multiple mutations in a clone of somatic cells

Mutation is a random process:

The number of mutations and the specific genes involved depends on the specific cell or tissue type under examination
The mutistep progression to malignancy in cancers of the colon and brain

A common sequence of mutational events in the progression to colon cancer or astrocytoma (astrocytes are supporting cells found in the nervous system).

Note the tissue becomes more disorganized as the tumor progresses to malignancy.
In addition to genes that function in growth promoting and growth inhibiting pathways, a third category of genes (not directly controlling rate of cell division) is mutated in cancer cells: *guardians of the genome*

What specific roles would these genes have?
Mutations in the DNA replication and repair machinery

Mutations in the feedback control machinery that prevents the cell from progressing through the cell cycle with damaged DNA

Nature 432: 316  Nov. 18, 2004
“All life on earth must cope with constant exposure to DNA-damaging agents such as the Sun's radiation. Highly conserved DNA-repair and cell-cycle checkpoint pathways allow cells to deal with both endogenous and exogenous sources of DNA damage. How much an individual is exposed to these agents and how their cells respond to DNA damage are critical determinants of whether that individual will develop cancer.** These cellular responses are also important for determining toxicities and responses to current cancer therapies, most of which target the DNA.  “

** see table on next page
Inherited cancer syndromes:

families with several cases of common cancers that fall into a recognized pattern of cancer types. Spectrum ranges from families with multiple cases at a young age to two to three cases at older ages.

Germline mutations (inherited from parent) predisposing individuals to cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>DNA repair defect</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeroderma pigmentosum</td>
<td>inability to repair bulky lesions that distort the DNA helix (such as UV-induced damage)</td>
<td>genome instability: point mutations skin cell death and skin cell cancers</td>
</tr>
<tr>
<td>Li Fraumeni syndrome (very rare)</td>
<td>loss-of-function in p53 gene normal p53 gene function is to stop/slow progression through the cell cycle in response to DNA damage and to stimulate apoptosis</td>
<td>multicancer syndrome: sarcomas, breast cancer, brain tumors</td>
</tr>
<tr>
<td>mutations in this gene also present in 50% of sporadic cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNPCC</td>
<td>defect in post-replication mismatch repair</td>
<td>genome instability: point mutations colon cancer</td>
</tr>
<tr>
<td>BRCA 1 &amp; 2</td>
<td>chromosome instability due to the inability to repair double-strand breaks in the DNA</td>
<td>genome instability: chromosome aberrations very high risk of breast cancer; increased risk of other cancers</td>
</tr>
</tbody>
</table>
# Classes of genes mutated in cancer cells

<table>
<thead>
<tr>
<th>Proto-oncogenes (becomes oncogene when mutated)</th>
<th>Tumor suppressor genes</th>
<th>Guardians of the genome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect of normal gene on cell growth and division</strong></td>
<td>Stimulates/Activates</td>
<td>Inhibits/Represses</td>
</tr>
<tr>
<td><strong>Oncogenic mutation in gene</strong></td>
<td>Gain-of-function</td>
<td>Loss-of-function</td>
</tr>
<tr>
<td>increased or unregulated activity or expression of the gene or gene product (hyperactive gene or product)</td>
<td>gene product is absent or its expression or activity is decreased</td>
<td></td>
</tr>
<tr>
<td><strong>Genetic behavior of oncogenic mutation</strong></td>
<td>Dominant</td>
<td>Recessive</td>
</tr>
<tr>
<td>One mutant allele is sufficient for the cancer phenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phenotypic effect of oncogenic mutation</strong></td>
<td>Increased stimulation of cell proliferation</td>
<td>Decreased inhibition of cell proliferation</td>
</tr>
<tr>
<td></td>
<td>CANCER</td>
<td>CANCER</td>
</tr>
</tbody>
</table>
Diagrams like this mistakenly imply an inevitable progression towards cancer:

**Figure 17.21** Cancer is thought to arise by successive mutations in a clone of proliferating cells.
Cancers seem to “progress” for the same reason the evolution of organisms seems to progress: *we only see the “successes” not the failures*
Genetic instability and tumor production. Cells that maintain an “optimal” level of genetic instability may be the most successful in the race to form a tumor.

a) In normal cells, the intrinsic amount of genetic instability is low. When such normal cells hit a selection barrier - low levels of oxygen or a scarcity of proliferation signals, for example -- they are very unlikely to be mutable enough to produce a cell that continues to proliferate.

b) In tumor cell precursors, an increased level of genetic instability makes it likely that at least one cell will contain the requisite genetic alteration to pass the selection barrier and continue the process of tumor progression. This genetic instability is retained in the lineage and can be measured in the resulting tumor.

c) If the level of genetic instability is too high, many of the cells suffer deleterious mutations and either proliferate more slowly than their neighbors or are eliminated by cell death. This excessive mutability can lead to extinction of the cell lineage.
Scientific American July 2003

Untangling the Roots of Cancer:

See alternative models for the genetical “development” of a cancer cell:
http://fire.biol.wwu.edu/trent/trent/cancermodels.pdf
Spectral karyotyping. This metaphase image of a breast cancer cell line (below) was obtained by 24-colour fluorescence *in situ* hybridization. Each chromosome is labelled with a different combination of fluorescent dyes and the final image is interpreted by software that colours each pixel to show which chromosome is most likely to be present at that point.

Remarkable genomic instability.

See Text figure 8-13  NORMAL karyotype
Chromosome painting by in situ hybridization with different-labelled probes
The probes used for the two different karotypes are obviously different
DIGRESSION:

_in situ:_ in the natural or the original position

**hybridization:** complementary base pairing of single-stranded nucleic acids to form a double stranded nucleic acid

1. the fluorescent probe is the DNA clone containing the region of the chromosome with the molecular polymorphism
2. the probe base pairs with the corresponding region of the chromosomal DNA in the metaphase spread

➤ See text figure 10.6 for more details

http://www.slh.wisc.edu/cytogenetics/procedures/FISH/FISH.html
Apoptosis:
• cell death pathway that operates in multicellular organisms to eliminate damaged and potentially harmful cells
• Can be triggered by external or internal signals

Mutations that decrease the chance that a cell will undergo apoptosis cause cancers:
• a cell that cannot undergo programmed cell death has a much longer lifetime within which oncogenic mutations can occur
• the extensive chromosomal damage and the abnormal physiological changes that occur in tumor cells would normally trigger apoptosis and eliminate the aberrant cell
• in other words, suppression of apoptosis prevents the organism from getting rid of maverick cells
Figure 4 Schematic representation of two main steps that contribute to a spectrum of mutations leading to cancer development. If DNA damage is repaired efficiently, the likelihood of tumour development is low. If cells have mutations in DNA-damage-response signalling pathways — either sporadic or inherited — this will lead to enhanced genomic abnormalities. Cells with damaged DNA frequently arrest or do not survive, thus reducing the probability that they will progress to malignancy. Mutations in apoptosis pathways, DNA-damage, DNA-repair or mitotic-checkpoint pathways can permit the survival or continued growth of cells with genomic abnormalities, thus enhancing the likelihood of malignant transformation.
• Metazoan tissue and organ function depends absolutely on the ability of cells to properly interact and communicate with each other.
• A genetically damaged cell is potentially a rogue cell so it’s a good plan to get rid of such a cell by apoptosis (programmed cell death).
• What do the red and green signify with respect to mutations in the processes?