Introduction

Cancer is the uncontrolled growth of cells that have damaged DNA expression. The cancerous cells repeatedly divide, displacing normal tissue. The cancer or neoplasm may be either benign or malignant: a benign cancer stays confined to the tissue of origin, while malignant cancer can spread to other organs. The secondary growths or metastases are a serious complication to any treatment of the cancerous cells. A tumor is any space-filling group of cells that may or may not be cancerous. Benign growths or tumors are usually noted by adding the ending "-oma." For example, adenoma would be a benign growth of the adrenal cortex, a hormone-producing group of cells near the kidney. Malignant tumors are noted by adding "sarcoma" or "carcinoma." A malignance of the adrenal cortex would be an adenocarcinoma. Bone cancer would be osteosarcoma.

Toxicology informs us about cancer on two accounts. First, toxicology research provided insight into the causes of cancer and likelihood of developing cancer. Second, many cancer treatments have serious toxicological side effects. Cancer treatment must often balance the need to kill the cancerous cells and the need to protect healthy cells.

Cancer - A Short History

The oldest descriptions of cancer date back to Egypt, at about 1600 BC. The so-called Edwin Smith Papyrus describes eight cases of what appears to be breast cancer. The tumors of the breast were treated by cautery, with a tool called "the fire drill." The first occupational association with cancer was noted in 1700 with the observation that nuns had an elevated incidence of breast cancer. In 1775, the English physician and surgeon Percivall Pott made the observation that exposure to soot might explain the high incidence of scrotum cancer in chimney sweeps. This was the first indication that exposure to chemicals, in this case a complex mixture, could cause cancer. However, this new knowledge did not immediately translate into improved working conditions for chimney sweeps. Over 100 years later it was observed that cancer of the scrotum was rare in continental Europe but still high in England, possibly due to better hygiene practices in Europe. We still have not taken to heart the cancerous consequences of exposure to smoke and tar, as ongoing consumption of tobacco products clearly shows. (Photo: chimney sweep in the 1850s.)
The industrial revolution of the late 19th and early 20th centuries brought clear confirmation that occupational exposure to chemicals could cause cancer. The first indication came from increases in skin and bladder cancers associated with cutting oils and dyes. In 1895, bladder cancer was associated with workers in the aniline dye industry. Further worker-based studies found that exposure to specific chemicals could be responsible for the cancer. In 1915, Japanese researchers reported that they could induce skin tumors in animals by repeatedly applying a coal tar solution to the skin of rabbits. These early studies, subsequently repeated with mice, ushered in the scientific investigation of the chemical causes of cancer. These studies also initiated the systematic investigation of the adverse health effects of chemicals, which in many ways laid the foundation for the toxicological sciences.

But chemicals are not the only cause of cancer. Marie Curie, awarded Nobel Prizes in both physics and chemistry, discovered radium in 1898. The green glow of radium fascinated people, and many thought it was a cure for many diseases, including cancer. The carcinogenicity of radium became tragically apparent when young women developed bone cancer from painting watch dials with radium. The use of nuclear weapons by the U.S. military in World War II, and subsequent development of the defense and nuclear industries in various countries, have raised public awareness of the health consequences of radiation exposure. Naturally occurring background radiation, as well as our many medical and industrial exposures to radiation, is responsible for some cancers. (Photo: Marie Curie in 1911.)

More recent research has broadened our understanding of cancer’s causes. Epidemiology studies of various human populations indicated that inorganic metals such as arsenic and nickel could cause cancer; this was subsequently confirmed in animal studies. Various hormones are implicated in organ-specific cancer, such as breast cancer. Nutrition and diet also appear to be related to cancer, specifically high caloric intake. The grain contaminant aflatoxin B1 is known to cause liver cancer. Chemical mixtures or exposure to multiple agents can increase the incidence of cancer; for example, smoking and asbestos exposure increase the likelihood of lung cancer. And finally, we are now learning that our genetic makeup increases the likelihood that certain cancers will develop. For example, breast cancer is linked to specific genes.

**Selected History of Cancer**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cancer Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1775</td>
<td>Scrotal Cancer</td>
<td>Soot</td>
</tr>
<tr>
<td>1822</td>
<td>Skin Cancer</td>
<td>Arsenic</td>
</tr>
<tr>
<td>1879</td>
<td>Lung Cancer</td>
<td>Uranium Mining</td>
</tr>
<tr>
<td>1895</td>
<td>Bladder Cancer</td>
<td>Aniline Dyes</td>
</tr>
<tr>
<td>1902</td>
<td>Skin Cancer</td>
<td>X-rays</td>
</tr>
<tr>
<td>Year</td>
<td>Cancer Type</td>
<td>Cause</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>1908</td>
<td>Leukemia</td>
<td>Filterable Agents</td>
</tr>
<tr>
<td>1914</td>
<td>Experimental induction of skin cancers</td>
<td>Coal Tar</td>
</tr>
<tr>
<td>1928</td>
<td>Experimental induction of skin cancers</td>
<td>UV Light</td>
</tr>
</tbody>
</table>

**Cancer Case Studies**

**Soot**

In 1775, Percivall Pott observed that there was an increased incidence of scrotum cancer in chimney sweeps and suggested that soot might be the cause. This was the first linking of occupational chemical exposure to cancer. Unfortunately this understanding was not translated into action and prevention. By the late 1890s, scrotal cancer was relatively rare on the European continent but still high in England, which some suggested was due to poor hygiene: failure to remove the soot from the skin resulted in chronic exposure to the chemicals in soot, which resulted in cancer. This example recalls the most basic tenets of public health: wash your hands (or other body parts).

Scientific investigation of the cancer-causing properties of soot took a step forward when Japanese research found that skin tumors developed if coal tar was repeatedly applied to the skin of rabbits. In the 1930s polycyclic aromatic hydrocarbons were isolated from coal tar and demonstrated to be carcinogenic. Despite this evidence, millions of people continue to expose themselves to the soot from tobacco and suffer from the resulting lung cancer.

**Benzene**

Benzene, C₆H₆, is a clear, colorless liquid at room temperature that readily evaporates. It is derived from petroleum and is widely used in the production of other products such as rubber, nylon, synthetic fiber, lubricants, glues, detergents, dyes, drugs, and pesticides, to name just a few. Worldwide, benzene use and production are measured in the billions of pounds, making it one of the top twenty chemicals in use. In the United States, benzene is present in gasoline at about 2%, but in other countries the amount may be up to 5%.

Benzene is classified as a human carcinogen. Liver enzymes convert benzene to more toxic metabolites; this mechanism is thought to be what causes its carcinogenicity. Benzene is readily absorbed by inhalation, and acute exposure can result in central nervous system effects such as dizziness, drowsiness, and eventual unconsciousness. Chronic exposure to benzene affects the bone marrow by crippling blood cell production, causing anemia, which can ultimately result in leukemia. At one time benzene was widely used as a solvent, resulting in excessive worker exposure; it continues to be a significant workplace contaminant. Benzene is present in the indoor environment from off-gassing of glues, synthetic materials, and tobacco smoke. Smokers can have benzene body burdens ten times that of nonsmokers. Because of its widespread use in industry, benzene is a common contaminant of hazardous waste and old industrial sites. The US EPA recommends the benzene not exceed 5 ppb
(parts per billion or 0.005 mg/L) in drinking water. The US Occupational Health and Safety Administration set a standard of 1 ppm of benzene in the air over an 8-hour period with an action level set at 0.5 ppm in an effort to encourage reductions in the workplace environment. Other agencies have established even lower standards down to 0.1 ppm benzene in the air.

**Asbestos**

Asbestos, a recognized human carcinogen, has a long and curious history. Asbestos continues to cause serious human health effects and continues to be the subject of legal action against companies that used or produced it.

Asbestos is the common name given to a group of six different naturally occurring fibrous minerals that can be separated into long fibers that can be spun and woven. The material is strong, flexible, resistant to heat and most solvents and acids, making it a very useful industrial product. Knowledge of asbestos goes back to the 2nd century B.C., but the first recorded use of the word asbestos was in the 1st century A.D. by Pliny the Elder.

The fire-resistant properties of asbestos were recognized early and contributed to its derivation from the Greek *sbestos* or "extinguishable," thus a*-bestos or inextinguishable. The Romans used asbestos to make cremation cloths and lamp wicks and in the Middle Ages, knights used asbestos to insulate their suits of armor. The use of asbestos increased with the Industrial Revolution and the need for a material to insulate steam boilers, such as those in locomotives. The first asbestos mine opened in 1879 in Quebec, Canada. Canada continues to be the world's largest producer of asbestos, followed by Russia, China, Brazil and several other countries. In the United States, California produces a small amount but the majority of the asbestos used in the United States is imported from Canada.

Serious lung disease associated with asbestos inhalation was first described in the early 1900s in England. This disease became known as asbestosis and was fully described in British medical journals in 1924 as young workers died from asbestos exposure. By the early 1930s, dose-related injury, length of time exposed, and the latency of response were being well characterized in both Europe and the United States. By the mid and late 1930s the first associations with lung cancer were documented. In the 1960s the consequences of asbestos exposure for many workers in World War II started to become evident. Mesothelioma, a cancer of the lining of the lung, was found to be almost exclusively associated with asbestos exposure.

In the United States, regulation of asbestos exposure started in the early 1970s, with exposure limits rapidly decreasing as the serious and latent consequences of asbestos exposure became apparent. White asbestos or chrysotile was used in thousands of consumer products and is common in many older homes. The serious health effects of asbestos exposure have resulted in both regulatory and legal action, and many countries have instituted complete bans on asbestos use.

**Radon**

Radon is another example of a very curious and toxic compound that many of us regularly inhale, one hopes in small amounts. For those regularly exposed to radon, there is an increased risk for lung cancer and for those who smoke, radon exposure results in a three-fold increase in the incidence of lung
cancer. In the United States it is estimated that indoor radon exposure causes between 7,000 and 30,000 lung cancer related deaths each year, second only to tobacco smoking.

Radon-222 is a colorless and odorless radioactive gas that results from the decay of Radium-226, which is widely distributed in the earth's crust. Radon decays with a half-life of 3.8 days into solid particles of polonium. It is actually the breakdown of polonium that causes cancer: polonium sticks to the tissues of the lung, and when it decays it releases an alpha particle, which damages the DNA of the closest cell.

Lung diseases, possibly related to radon, were first reported in the 1400s, and in 1879 lung cancer was seen in European miners. Radon was discovered several years later in 1900 by the German chemist Friedrich Ernst Dorn. Regulation of workplace exposure began in the 1950s and subsequent studies of underground mine workers in Canada, Czechoslovakia, France, Australia, Sweden and the United States have allowed researchers to develop very sophisticated models of the cancer-causing effects of radon. It is difficult to translate these results into the effects of radon on indoor home exposure. The United States EPA sets an action level of four picocuries per liter (pCi/l). There are some areas of the United States and Europe with high levels of radon that can enter homes, schools or public buildings, particularly underground levels. In the United States, it is estimated that 1 in 15 (6%) of homes have elevated levels of radon. A number of public and private organizations provide information on reducing indoor radon exposure.

See the References and Additional Information page for links to information on benzene, asbestos, and radon.

**Genetic Toxicology and the Biology of Cancer**

Genetic toxicology is the study of the effects of chemical and physical agents on genetic material. It includes the study of DNA damage in living cells that leads to cancer, but it also examines changes in DNA that can be inherited from one generation to the next. Genetic toxicology, although not called that at the time, got its start in 1927 when American geneticist Hermann J. Muller (1890-1967) demonstrated that X-rays increased the rate of gene mutations and chromosome changes in fruit flies.

The relevance of genetic toxicology is clearly evident from inheritable diseases such as phenylketonuria (an inability to metabolize phenylalanine), cystic fibrosis (lung disease), sickle cell anemia, and Tay-Sachs disease. Recent advances in molecular biology and genomic sciences are leading to a far greater understanding of the genetic cause of disease and even pointing the way to treatments.

**DNA Mutations**

To understand cancer it is necessary to explore the cellular changes that turn a normal cell into a malignant cell that repeatedly and uncontrollably divides. This transformation occurs when there is genetic damage or an alteration in the structure of a cell's DNA.

DNA, short for deoxyribonucleic acid, is the coding machinery of life. The beauty of DNA is its simplicity. The double helix of DNA is made of the compounds adenine (A), guanine (G), thymine (T), and cytosine (C). These chemicals are bound in long stretches as AT and CG pairs, and wrapped in sugar molecules
that hold them together. Long stretches of these AT and CG combinations form genes which when "read" produce the proteins that drive our cells.

Ideally the DNA sequence would not change except in the recombining that occurs during reproduction. However, DNA damage occurs regularly as part of the cell process, and from interaction with both normal cellular chemicals and with toxic chemicals. A very robust repair mechanism rapidly and very accurately repairs the DNA damage, but if for some reason the DNA is repaired incorrectly, a mutation occurs. The mutation is a subtle or not-so-subtle change in the A, G, C, or T that make up the DNA.

Many of the mutations have no effect, some have minor effects, and a small number have life-threatening effects. If a mutation occurs in the wrong place, a cell can start to divide uncontrollably, becoming a malignant cell and causing a cancer. If a mutation occurs in our germ line cells, the mutation can be passed on to our offspring.

**Mutagens**

Chemicals that induce mutations in the DNA are called mutagens, and when these changes lead to cancer the chemical is called a carcinogen. Not all mutagens are carcinogens, and not all carcinogens are mutagens. In 1946 it was shown that nitrogen mustards (derived from mustard gas first used by the military in 1917 during WWI) could induce mutations in the fruit fly and reduce tumor growth in mice. Genetic toxicology developed ways to test chemical and physical agents for their mutagenic properties, and in the 1970s, Bruce Ames and others developed a cellular-based test for genetic mutations. This test became known as the Ames assay. Sophisticated variations of these tests are now required by many government regulatory agencies to test chemicals for mutagenicity before they are approved for use. Often it is a metabolite (breakdown product) of the compound that causes cancer, not the original compound. Ideally, a foreign chemical is made less toxic when metabolized, but sometimes a chemical can be made more toxic. This more-toxic chemical can then interact with cellular DNA or proteins and produce malignant cells. This process is called bioactivation. It is also possible for a chemical to encourage bioactivation or to accelerate the development of cancer. Many variations of the Ames test that include liver cells were developed to simulate the metabolism of the chemical in the liver and determine if bioactivation would result in mutations.

Efforts to understand the underlying biology of cancer are ongoing. The genomic sciences are helping to explain why some people are more susceptible to cancer than others. We also know that there are many causes of cancer and that we can reduce the likelihood of developing cancer.

**What Causes Cancer?**

We are continuously exposed to a wide range of chemical and physical agents, both natural and human-generated, that may cause cancer. Exposure to sunlight, background radiation, natural and manufactured chemicals, even oxygen can damage our DNA and result in cancer. Because our knowledge is imperfect, there is a great deal of conflicting information on the causes of cancer and what can be done to reduce the risk of developing cancer. And we are just beginning to understand how our individual genetic makeup influences the possibility of developing cancer and other genetic-based disease.
## Some Known Causes of Cancer

<table>
<thead>
<tr>
<th>Cause</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td>Tobacco and alcohol consumption, diet</td>
</tr>
<tr>
<td>Ambient environmental exposures</td>
<td>Air, drinking water</td>
</tr>
<tr>
<td>Organic chemicals</td>
<td>Benzo(a)pyrene (in coal tar), Benzene</td>
</tr>
<tr>
<td>Inorganic chemicals and metals</td>
<td>arsenic, cadmium, nickel</td>
</tr>
<tr>
<td>Fibers</td>
<td>Asbestos</td>
</tr>
<tr>
<td>Radiation</td>
<td>Sunlight (ultraviolet), radioactive material</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diethylstilbestrol (DES)</td>
</tr>
<tr>
<td>Viruses</td>
<td>Epstein-Barr, AIDS, papilloma</td>
</tr>
<tr>
<td>Genetic</td>
<td>Increased likelihood (ex. breast cancer)</td>
</tr>
</tbody>
</table>

Lifestyle choices are the cause of many cancers. Tobacco consumption probably accounts for between 25 to 40% of all cancer deaths. The other major lifestyle choices associated with cancer are alcohol consumption and diet. Alcohol increases the incidence of liver disease and liver cancer. Diet has a broad range of effects, some good and some not so good. Some cooked meats have a higher concentration of agents that appear to cause cancer; however, a diet rich in vegetables may reduce the incidence of cancer. High caloric intake and high fat consumption may encourage the onset of cancer from other agents.

Numerous organic chemicals are known or likely carcinogens. In the 1930s, benzo(a)pyrene was isolated from coal tar and shown to cause skin cancer. Further investigation revealed an entire class of carcinogenic compounds called polycyclic aromatic hydrocarbons (PAHs). Shortly after World War II, it was discovered thatazo dyes could also cause cancer. In the 1960s, naturally occurring contaminants from a grain fungus (aflatoxin) were found to be a potent liver carcinogen.

Inorganic chemicals and fibers are also carcinogenic. Arsenic is the most serious human carcinogen because of exposure from drinking water. Cadmium, chromium, and nickel are all lung carcinogens. The most common lung carcinogen is asbestos, which has unique properties making it ideal for many industrial and even home insulation applications. It was also used in shipyards and in car brake pads. This widespread use resulted in thousands of workers being exposed to asbestos and suffering from a range of lung diseases, including cancer. Asbestos exposure produces a very unique form of lung cancer called mesothelioma. Mesothelioma is caused in part by asbestos fibers inducing a chronic irritation of the lung, resulting in an inflammatory response that ultimately causes some cells to become cancerous. Hormones, which regulate many important bodily functions, are also associated with cancer. One of the first hints of the relationship between hormones and cancers was the observation that nuns had a
greater incidence of breast cancer. This was due to the nuns not having children. Since that time there have been numerous studies on the association of birth control, childbirth, and most recently, hormone replacement, with cancer. In males there is ongoing study of hormones and prostate cancer. While it is clear that hormones and cancer are related, the exact characterization of this relationship is still unclear.

We are becoming increasingly aware of the importance of diet and nutrition in reducing the risk of cancer. From a toxicological perspective, it is important to reduce exposure to agents that increase the risk of cancer. Cancer, like declining physical and mental ability, is related to old age and may even be a natural consequence of the aging process. However, exposure to cancer-causing agents increases the risk or likelihood of developing cancer.

**Cancer - Regulatory Standards**

National and international agencies have established systems to classify agents according to the likelihood that the agent may cause cancer. This is often a difficult process because the information on an agent may be incomplete or inconclusive. Data from any human epidemiology studies are evaluated first, followed by information from animal studies. The International Agency for Research on Cancer (IARC) has developed one of the most comprehensive classification schemes. In this scheme an agent is rated from 1 to 4 based on human and animal data (see table below). Other classification schemes are in use by the U.S. EPA, National Toxicology Program, National Institute of Occupational Health Sciences (NIOSH), and the State of California.

**IARC Classification Scheme for Carcinogenicity of Chemical and Physical Agents**

<table>
<thead>
<tr>
<th>Group</th>
<th>Evidence</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Carcinogenic to humans</td>
<td>Sufficient human data</td>
<td>Aflatoxin, benzene, arsenic, formaldehyde</td>
</tr>
<tr>
<td>2A. Probably carcinogenic to humans</td>
<td>Limited human data</td>
<td>PCBs, styrene oxide, creosotes</td>
</tr>
<tr>
<td></td>
<td>Sufficient animal data</td>
<td></td>
</tr>
<tr>
<td>2B. Possibly carcinogenic to humans</td>
<td>Limited or inadequate human data</td>
<td>Styrene, TCDD-dioxins, lead, Mirex</td>
</tr>
<tr>
<td></td>
<td>Sufficient animal data</td>
<td></td>
</tr>
<tr>
<td>3. Not classifiable as to its carcinogenicity to humans</td>
<td>No enough human or animal data</td>
<td>Diazepam, melamine, phenol</td>
</tr>
<tr>
<td>4. Probably not carcinogenic to humans</td>
<td>Inadequate human data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inadequate animal data</td>
<td></td>
</tr>
</tbody>
</table>

(Source: IARC - Preamble to the IARC Monographs, 2006)
Government regulatory agencies do not always agree on the classification of cancer-causing compounds and there are several different schemes, used by different agencies. Elaborate animal study protocols are used to determine if an agent may cause cancer.

**Cancer - Recommendation and Conclusions**

While scientists have made great strides in understanding the causes of cancer and developing treatments, there will always be a risk for developing cancer. The likelihood of developing cancer is related to our individual sensitivity and our dose/response curve. As individuals, we can try to be aware of the risks of exposure to suspected carcinogens and take appropriate actions to reduce our exposure, but this can be difficult due to a lack of ingredient labeling. There must be better labeling of ingredients and easier access to information about chemicals that may be carcinogenic.

**Cancer - References and Additional Information**

**European, Asian, and International Agencies**

  IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control.
  Site has information on international exposure to a wide range of compounds that cause cancer.
  Site has information on the treatment and cause of cancer for Japan (Japanese or English versions available).
  An Australian site that focuses on skin cancer and its primary cause, the sun.
  "The Cancer Council Victoria is an independent, volunteer-based charity whose mission is to lead, coordinate, implement and evaluate action to minimize the human cost of cancer for all Victorians."
  The Asbestos Institute is dedicated to promoting the safe use of asbestos in Canada and throughout the world. (French and English.)
Provides a free information service about cancer and cancer care for people with cancer and their families.

**North American Agencies**

**General Information on Cancer**
  Oncology Tools contains a variety of information related to cancer and approved cancer drug therapies.
  EPA cancer risk assessment guidelines.
  Applying science to improve risk assessment and environmental decision making.
  The NCI, established under the National Cancer Act of 1937, is the Federal Government's principal agency for cancer research and training.
  The CDC monitors cancer incidence and promotes cancer prevention and control.
  This site provides interactive maps, graphs (which are accessible to the blind and visually-impaired), text, tables, and figures showing geographic patterns and time trends of cancer death rates for the time period 1950-1994 for more than 40 cancers.
  A service of the US National Cancer Institute, CSI is a "source for the latest, most accurate cancer information for patients, their families, the general public, and health professionals."

**Benzene Information**
  Hazard fact sheet on benzene.
  See fact sheets and case studies in environmental benzene.

**Asbestos Information**


**Radon Information**

• **US Environmental Protection Agency (EPA).** Online: <http://www.epa.gov/radon/index.html> (accessed: 07 July 2009). USEPA has extensive information on radon exposure in the U.S.


**Non-Government Organizations**

• **The American Cancer Society (ACS).** Online: <http://www.cancer.org/> (accessed: 07 July 2009). The ACS is a nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives, and diminishing suffering from cancer through research, education, advocacy, and service.

• **American Association for Cancer Research (AACR).** Online: <http://www.aacr.org/> (accessed: 07 July 2009). "AACR accelerates progress toward the prevention and cure of cancer by promoting research, education, communication, and collaboration."

• **Children's Cancer Association.** Online: <http://www.childrenscancerassociation.org/> (accessed: 07 July 2009). Provides information and resources regarding childhood cancer.


• **National Radon Safety Board (NRSB).** Online: <http://www.nrsb.org/> (accessed: 07 July 2009). "The NRSB seeks to encourage the highest standards of practice and integrity in radon services through the development of independent standards and procedures for certifying, approving and accrediting radon testers, mitigators, measurement devices, chambers and laboratories."

Site has information on radon in the home environment as well as tobacco and asthma.

  EMS fosters research on the basic mechanisms of mutagenesis as well as on the application of this knowledge in the field of genetic toxicology.

  PRCI is a comprehensive treatment center with a focus on prevention and education.