

A Small Dose of Cancer and Genetic Toxicology Or An Introduction to Cancer and Genetic Toxicology

Chapter 24

A Small Dose of Toxicology - The Health Effects of Common Chemicals

ED3 – Revised October 2020

By

Steven G. Gilbert, PhD, DABT

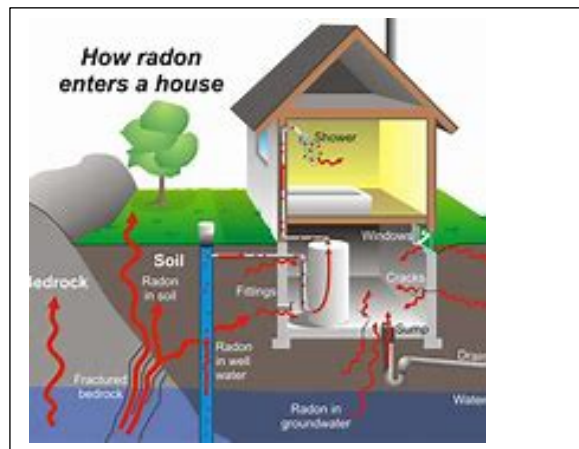
Institute of Neurotoxicology & Neurological Disorders (INND)

Seattle, WA 98115

E-mail: sgilbert@innd.org

Supporting web site:

web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"



What is cancer?

Cancer is an unwelcome, potentially life-threatening diagnosis that one third of us will experience. The oldest descriptions of cancer date back to Egypt 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 cauterization, with a tool called "the fire drill." Clearly there was a desire and need to treat this dreaded disease but the conclusion was "There is no treatment." It is only in the last 100 years that we have developed more sophisticated tools to treat cancer.

We now know much more about cancer, its causes and treatment. Technically 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 malignancy 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 of the treatments of cancer have serious toxicological side effects. Cancer treatment must often balance the need to kill the cancerous cells without harming the normal cells of the body.

Initially, our understanding of cancer was advanced entirely by humans, the ultimate experimental subject. 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 very astute observation that exposure to soot might explain the high incidence of cancer of the scrotum in chimney sweeps. This was the first indication that exposure to chemicals, in this case a complex mixture, could cause cancer. 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.

The industrial revolution of the late 19th and early 20th century 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 cause of cancer. These early animals studies initiated the systematic investigation of the adverse effects of chemicals, which in many ways laid the foundation for the toxicological sciences.

But chemicals are not the only cause of cancer. During this incredible period of time, researchers such as Marie Curie (1867-1934) were discovering radioactivity, and in 1895 Wilhem Conrad Roentgen discovered X-rays. Marie Curie was ultimately awarded Nobel Prizes in both physics and chemistry, the only person ever so honored. One of her discoveries was 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 (for more details see the radiation chapter). The use of nuclear weapons by the U.S. military and subsequent development of the defense and nuclear industries has made us all well aware of the consequence of radiation exposure. Naturally occurring background radiation combined with our many medical and industrial exposures to radiation is responsible for some cancers.

Table 19.1 Selected History of Cancer

Year	Cancer type	Cause
1775	Scrotal Cancer	Soot
1822	Skin Cancer	Arsenic
1879	Lung Cancer	Uranium Mining
1895	Bladder Cancer	Aniline Dye
1902	Skin Cancer	X-rays
1908	Leukemia	Filterable Agent
1914	Experimental Induction of Skin Cancers (rabbit)	Coal Tar
1928	Experimental Induction of Skin Cancers	UV Light

As our observational powers improved so did our appreciation of what causes cancer. Epidemiology studies of various human populations indicated that inorganic metals such as arsenic and nickel could cause cancer. This was subsequently confirmed in laboratory studies with animals. 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.

Our cells and bodies have evolved to fight off cancer. Specific DNA repair mechanisms work to correct damaged DNA. Our immune system works to isolate and kill rogue cancer cells. Cancer appears to be part of life, an aspect of the aging process, even bad luck. Clearly, however, we have learned that reducing our exposure to certain chemical and physical agents can decrease the likelihood of developing cancer or at least delay its onset.

Causes of cancer

Organic chemicals (alcohol, tars, dyes, solvents)

Inorganic agents (metals – arsenic, nickel ...)

Hormones

Nutrition (diet, fat, high calories)

Tobacco products

Chemical mixtures

Genetics

Case Studies

Soot

In 1775, Percivall Pott observed that there was an increased incidence of cancer of the scrotum 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 hydrocarbon was 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 and readily evaporates into the air. 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 20 chemicals in use. In the United States, benzene is present in gasoline at about 2% but in other countries may be up to 5%. It is readily absorbed by inhalation. Acute exposure can result in central nervous system effects such as dizziness, drowsiness and eventual unconscious. Liver enzymes convert benzene to more toxic metabolites, which is thought to be the mechanism for the carcinogenic effects of benzene. It is one of the few compounds classified as a human carcinogen. 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 out-gassing of glues, synthetic materials, and tobacco smoke. Smokers can have benzene body burdens 10 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-sbestos 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 along 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 1900's 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 in many countries the total banning of the use of asbestos.

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 that smoke radon exposure results in a 3-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 break down of polonium that causes cancer. Polonium sticks to the tissues of the lung, and when it decays an alpha particle is released which damages the DNA of the closest cell, ultimate causing lung cancer. 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 a home, schools or public building, particularly the below ground 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.

Biology of Cancer and Genetic Toxicology

Cancer is the result of a cell's machinery going horribly out of control. In its simplest form, there is a permanent change a cell's DNA that allows that cell to repeatedly divide, passing this change along to the next cell. 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.

Genetic toxicology is the study of the effects of chemical and physical agents on genetic material. Genetic toxicology includes the study of DNA damage in living cells that leads to cancer but also changes in DNA that can be inherited from one generation to the next. The relevance of genetic toxicology is clearly evident from inheritable diseases such as phenylketonuria (an ability to metabolize phenylalanine), cystic fibrosis (lung disease), sickle cell anemia, or Tay-Sachs disease. Recent advances in the molecular biology and genomic sciences are leading to a far greater understanding of the genetic cause of the disease and even pointing the way to treatments.

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. At that time Muller and others were investigating how naturally occurring changes in the genes related to structural changes in the fruit fly. The rapidly reproducing and short-lived fruit fly was an excellent subject, but waiting for the spontaneous changes to occur in their genes—at that time they did not yet know about DNA—was slow. Muller used X-rays to increase the rate of change in genes, thus furthering his research efforts but also demonstrating an important toxicological property of X-rays. As our knowledge of biology deepened, it was discovered how the energy of X-rays caused changes in the DNA.

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

Typical short strand of DNA

G C A G C A T
C G T C G T A

When sequences of G, C, A, and T are read (by RNA), they are translated into other chemicals that eventually become proteins. Ideally the DNA sequence would not change except in the recombining that occurs during reproduction. However, a cell's DNA is

located in the very dynamic and demanding environment of the cell, where damage can occur. DNA damage occurs regularly as part of the cell process and from interaction with normal cellular chemicals as well as toxic chemicals. Fortunately, there is a very robust repair mechanism that rapidly and very accurately repairs the DNA damage. However, if for some reason the DNA is repaired incorrectly, a mutation occurs. The mutation is a subtle or even not-so-subtle change in the A, G, C, or T that make up the DNA.

Normal strand of DNA --- Mutated Strand	
G C A G C A T	G C A A C A T
C G T C G T A	C G T T G T A

Many of the mutations have no effect, some have minor effects, and even a smaller 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 it can be passed on to our offspring. Muller used X-rays to induce many mutations, some of which would be in the germ line cells of fruit fly and thus passed on to the next generation, which he could study.

Chemicals can damage the DNA and induce mutations. 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, but in general it is best to avoid 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 reduces tumor growth in mice. As the relationship of gene mutations to cancer become evident, genetic toxicology developed ways to test chemical and physical agents for their mutagenic properties. In the 1970s these tests were greatly simplified when Bruce Ames and others developed a cellular-based test for genetic mutations. This test became know as the Ames assay. Sophisticated variations of these tests are now required by many government regulatory agencies to test for the mutagenicity of a chemical before approval for use. For example, you would not want an artificial sweetener to cause mutations even at a very low rate.

Often it is not the parent compound that causes the cancer but instead a metabolite of the original compound. Ideally, a foreign chemical is made less toxic by metabolism, 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 that another chemical may encourage bioactivation or possibly interact to accelerate the development of a cancer. This knowledge influences the test required of chemicals because some were not mutagens until metabolized by liver enzymes. Many variations of the Ames test were developed that include liver cells to simulate the metabolism of 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?

The causes of cancer are varied: many known, most likely multiple, many unknown, and just a random event of no specific cause. We are continuously exposed to a wide range of chemical and physical agents, from both natural- and human-generated sources that may cause cancer. Because our knowledge is not perfect 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. We are just beginning to understand how our individual genetic makeup influences the possibility of our developing cancer and other genetic-based disease. In the future we will have even more knowledge about how the environment will interact with our genetics to cause cancer. We will briefly examine some of the known causes of cancer (Table 19.2).

Table 19.2 Exposure to Cancer Causing Agents

Cause	Example
Lifestyle	Tobacco consumption – drinking alcohol – diet
Environmental exposures	Air, drinking water
Organic chemicals	Benzo(a)pyrene (in coal tar), benzene
Inorganic chemicals and metals	Arsenic, cadmium, nickel
Fibers	Asbestos
Radiation	Sun (ultraviolet), radioactive material
Drugs	DES (diethylstilbestrol)
Viruses	Epstein-Barr virus, AIDS, papillomavirus
Genetic	Increased likelihood (breast cancer)

Lifestyle choices are the cause of many cancers. This is obvious from even a quick look at the correlation between tobacco consumption and lung cancer. The age-adjusted incidence of lung cancer for males peaked in the late 1980s and then started to decline with the decline in smoking. But for females, the increase in lung cancer appears to be peaking in the late 1990s and has yet to start declining. These data testify to the delayed onset of cancer and the relationship with tobacco consumption. Tobacco consumption probably accounts for between 25 to 40% of all cancer deaths.

The other major lifestyle choices associated with cancer are diet and alcohol consumption. Alcohol increases the incidence of liver disease and cancer. Diet has a

broad range of effects, some good and some not so good. Some cooked meats have a higher concentrations of agents that appear to cause cancer. On the other hand 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. As with most things, a high dose results in a greater response. In the most cases a high dose of calories, fat, alcohol or tobacco increases the likelihood of cancer.

Numerous organic chemical agents are known or highly likely to cause cancer. In the 1930s benzo(a)pyrene was isolated from coal tar and shown to cause skin cancer. Further investigation discovered an entire class of carcinogenic compounds called polycyclic aromatic hydrocarbons (PAHs) that caused cancer. Prior to World War II was a rich period of chemical synthesis. It was soon discovered that the azo dyes could also cause cancer. Naturally occurring contaminants from a grain fungus (aflatoxin) was found to be a potent liver carcinogen. A high incidence of liver cancer occurred when grain was poorly stored and people had liver disease such as hepatitis. People from hot and humid areas of Africa were particularly at risk for liver cancer from this grain fungus.

Inorganic chemicals and fibers are also carcinogenic. Arsenic is the most serious human carcinogen because of exposure from drinking water (see arsenic chapter). Cadmium, chromium and nickel are all lung carcinogens. The most common lung carcinogen is asbestos. The unique properties of asbestos made it ideal for many industrial and even home insulation applications. It was used in shipyards and in car brake pads. This widespread use resulted in thousand 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 the fibers inducing a chronic irritation of the lung resulting in an inflammatory response that ultimate results in some cells becoming cancerous.

Hormones regulate many important bodily functions and are also associated with cancer. One of the first hints of the relationship of hormones to cancers was the observation that nuns had a greater incidence of breast cancer. This was naturally related to the nuns not having children and now we know that may be hormone related. 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.

Who Is Vulnerable?

We are all vulnerable to cancer. Exposure to sunlight, background radiation, natural and manufactured chemicals, even oxygen can damage our DNA and result in cancer. We know that exposure to certain chemical or physical agents can increase the risk of developing cancer. There are many examples of workplace exposures resulting in cancer. Radon gas in coal and uranium mines can cause lung cancer. Asbestos exposure has affected thousand of workers and resulted in compensation claims from the companies. Of course, not smoking would result in the greatest reduction in cancers and other health related effects of tobacco.

The figures below illustrate the U.S. male and female cancer death rates from 1938 to 1998. The most striking changes, for both male and female are for lung cancer deaths, which also reflects the changes in cigarette smoking. The peaks in lung cancer correspond to the delay in onset of lung cancer after the start of smoking. The incidence of lung cancer in males is declining with the drop in tobacco consumption while that of females is just peaking.

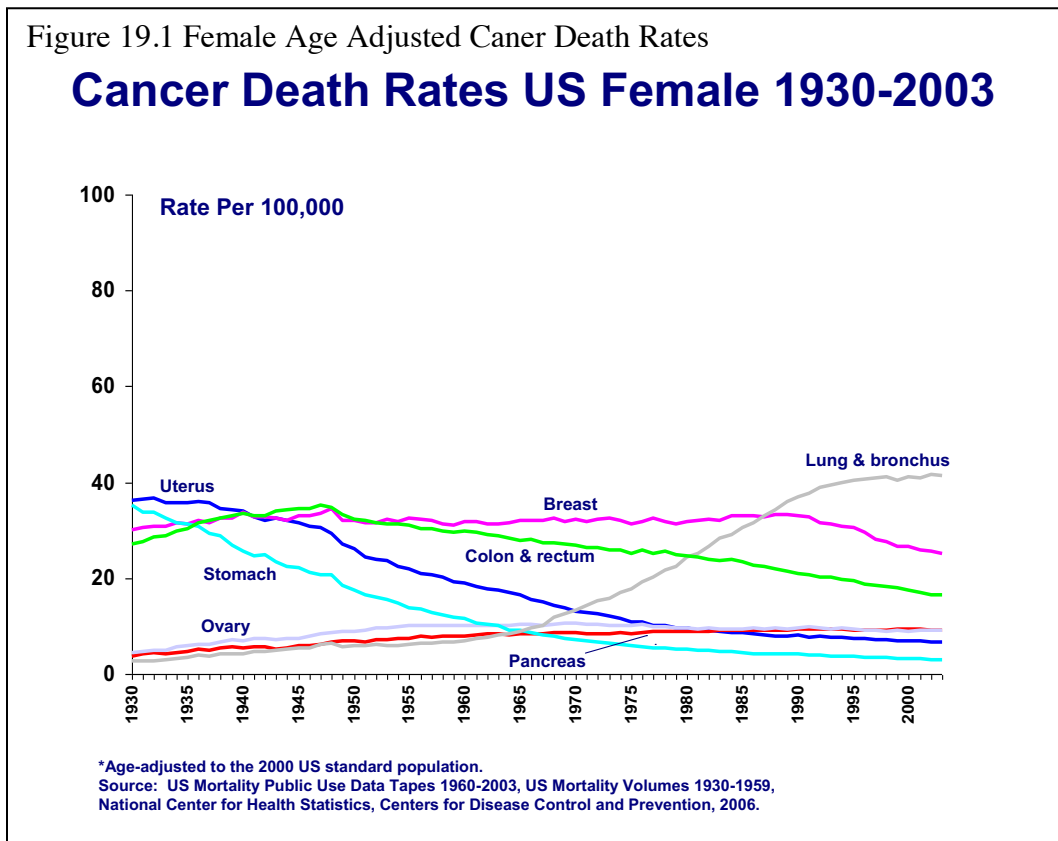
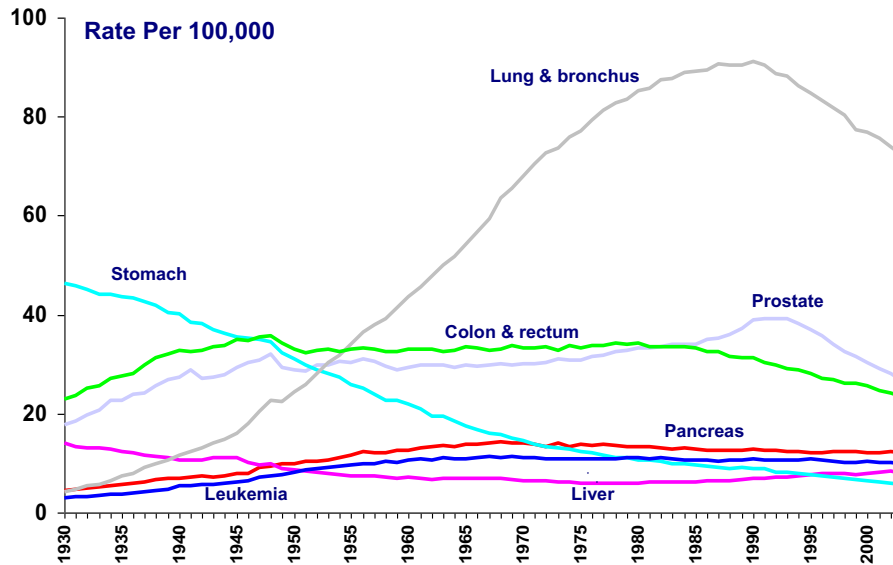


Figure 19.2 Male Age Adjusted Cancer Death Rates

Cancer Death Rates Male 1930-2003



*Age-adjusted to the 2000 US standard population.

Source: US Mortality Public Use Data Tapes 1960-2003, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

Advances in the genomic sciences will ultimately provide us with individual knowledge of our vulnerability to cancer. Some of these cancers are triggered by interaction of genes and environmental exposures. This knowledge will provide even more incentive to reduce or control exposure to specific agents.

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 and then 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 (Table 19.3). Other classification schemes are in use by the U.S. EPA, National Toxicology Program, NIOSH, and the State of California.

Table 19.3 IARC Classification Scheme for Human Carcinogenicity

Group	Evidence	Examples
1. Agent is human carcinogen	Sufficient human data	Aflatoxin, benzene, Arsenic
2A. Agent is probably a human carcinogen	Limited human data Sufficient animal data	PCBs, styrene oxide
2B. Agent is possibly a human carcinogen	Limited or inadequate human data Sufficient animal data	Styrene, TCDD
3. Agent is not classifiable as to a human carcinogen	Not enough human or animal data	Diazepam
4. Agent is probably not a human carcinogen	Inadequate human data Inadequate animal data	

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. As part of the approval process, government agencies require animal testing for carcinogenicity for new compounds entering the food supply. We want to be sure that the latest artificial sweetener will not cause cancer.

Recommendation and Conclusions

The war on cancer is really a long and never ending battle. While scientists have made great strides in understanding the causes of cancer and developing treatments, there will always be a risk for developing cancer. 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. The likelihood of developing cancer is related to our individual sensitivity and our dose / response curve. Less exposure means you will be less likely to develop cancer. Most importantly, there must be better labeling of ingredients and easier access to information about chemicals that may be carcinogenic.

More Information and References

Cancer & Genetic Toxicology presentation material and references online is available at www.asmalldoseoftoxicology.org

European, Asian, and International Agencies

- IARC - International Agency for Research on Cancer (IARC) - World Health Organization (WHO). Online: <<http://www.iarc.fr/>> (accessed: 18 October 2020).

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.

- World Health Organization (WHO) - Cancer. Online: < <https://www.who.int/news-room/fact-sheets/detail/cancer> > (accessed: 18 October 2020).
Site has information on international exposure to a wide range of compounds that cause cancer.
- Japan – National Cancer Center (English). Online: < <https://www.ncc.go.jp/en/ncch/index.html> > (accessed: 18 October 2020).
Site has information on the treatment and cause of cancer for Japan (Japanese or English version available).
- Cancer Research UK. Online: < <https://www.cancerresearchuk.org/about-cancer/type> > (accessed: 18 October 2020).
Provide a free information service about cancer and cancer care for people with cancer and their families.

North American Agencies

General Information on Cancer

- US Environmental Protection Agency (EPA) - National Center for Environmental Assessment (NECA). Online: <<http://cfpub.epa.gov/ncea/>> (accessed: 19 October 2020).
Applying science to improve risk assessment and environmental decision making.
- US National Cancer Institute (NCI). Online: <<http://www.cancer.gov/>> (accessed: 19 October 2020).
The NCI, established under the National Cancer Act of 1937, is the Federal Government's principal agency for cancer research and training
- US Centers for Disease Control and Prevention (CDC). Online: <<http://www.cdc.gov/cancer/>> (accessed: 19 October 2020).
The CDC monitors cancer incidence and promotes cancer prevention and control.
- US National Cancer Institute - NCI Cancer Atlas. Online: < <https://gis.cancer.gov/canceratlas/> > (accessed: 19 October 2020).
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.

Benzene Information

- US Environmental Protection Agency (EPA). Online: nothing
- US Agency for Toxic Substance Disease Registry (ATSDR). Online: < <https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14>> (accessed: 19 October 2020).
See fact sheets and case studies in environmental benzene.

Asbestos Information

- US Environmental Protection Agency (EPA). Online: nothing
- U.S. Cancer Information Service (CSI) - Asbestos Exposure and Cancer Risk. Online: < <https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/asbestos/asbestos-fact-sheet>> (accessed: 19 October 2020).
Extensive information on asbestos.
- US Agency for Toxic Substance Disease Registry (ATSDR). Online: < https://www.atsdr.cdc.gov/asbestos/health_effects_asbestos.html> (accessed: 19 October 2020).
See fact sheets and case studies in environmental asbestos.

Radon Information

- US Environmental Protection Agency (EPA). Online: <<http://www.epa.gov/radon/>> (accessed: 19 October 2020).
USEPA has extensive information on radon exposure in the U.S.
- U.S. Geological Survey (USGS). Online: < https://www.usgs.gov/faqs/what-radon?qt-news_science_products=0#qt-news_science_products> (accessed: 19 October 2020).
Maps and supply information on radon in the United States

Non-Government Organizations

- The American Cancer Society (ACS). Online: <<http://www.cancer.org/>> (accessed: 19 October 2020).
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: 19 October 2020).
“AACR accelerates progress toward the prevention and cure of cancer by promoting research, education, communication, and collaboration.”
- American Lung Association (ALA). Online: <<https://www.lung.org>> (accessed: 19 October 2020).
Site has information on radon in the home environment as well as tobacco and asthma.
- Roswell Park Cancer Institute (PRCI). Online: <<http://www.roswellpark.org/>> (accessed: 19 October 2020).
PRCI is a comprehensive treatment center with a focus on prevention and education.
- Fred Hutchinson Cancer Research Center (FHCRC) Online: <https://www.fredhutch.org> (accessed: 19 October 2020).
The mission of Fred Hutch is the elimination of cancer and related diseases as causes of human suffering and death.

Wikipedia

Cancer - <https://en.wikipedia.org/wiki/Cancer> - (accessed: 19 October 2020). Provides an overview with a list of cancer causes.

Cancer research - https://en.wikipedia.org/wiki/Cancer_research - (accessed: 19 October 2020).

Carcinogen - <https://en.wikipedia.org/wiki/Carcinogen> - (accessed: 19 October 2020).

Seminal papers-

The Hallmarks of Cancer, published in 2000, and Hallmarks of Cancer: The Next Generation, published in 2011, by Douglas Hanahan and Robert Weinberg. Together, these articles have been cited in over 30,000 published papers.