Module 12
Cancer and Biomarkers of Health

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Key Terms and Concepts

- agonist
- apoptosis
- B-cell
- benzene
- biological half-life
- biomarker
- cancer progression
- carcinogen
- contaminant
- dichlorodiphenyltrichloroethane (DDT)
- endocrine-disrupting chemicals (EDCs)
- epidemiology
- epigenetics
- estrogenic chemicals
- glycoprotein
- hyperplasia
- in vitro
- in vivo
- latency period
- malignant neoplasia
- metastasis
- mutagen
- neoplasia

- no observed effect concentration (NOEC)
- oncogene
- persistent organic pollutants (POPs)
- polycyclic aromatic hydrocarbon (PAH)
- procarcinogen
- proto-oncogene
- suppressor genes
- synergism
- xenobiotic

Learning Objectives/Outcomes

Upon completion of this module, you should be able to

1. explain what cancer is.
2. explain what biomarkers are?
3. explain what POPs and EDCs are?
4. explain the relationship between pollutants and cancer?

Overview

Cancer plays a large role in human society today because it kills millions of people around the world on a yearly basis. Thousands of people die from cancer every year in the Arctic regions of the world: Canada, Iceland, Norway, Sweden, Finland, Denmark, Russia, and Alaska (United States). It has been estimated by the American Cancer Society that 1,284,900 people in the United States alone will be diagnosed with cancer in the year 2002 and 1,334,100 in 2003. (See fig. 12.1a–b.)

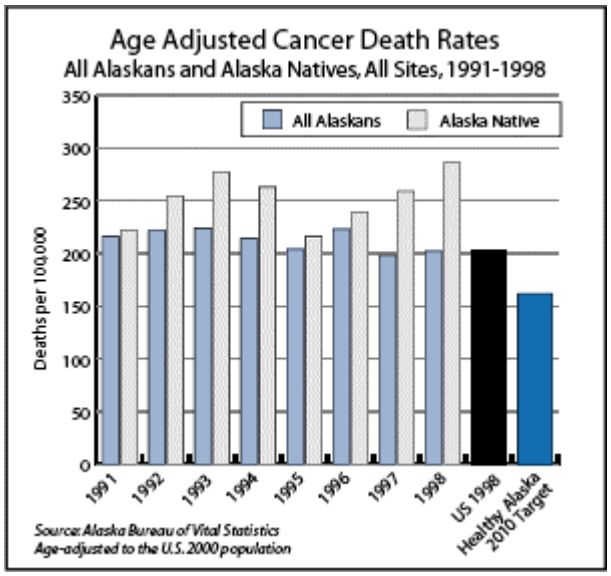

Fig. 12.1a

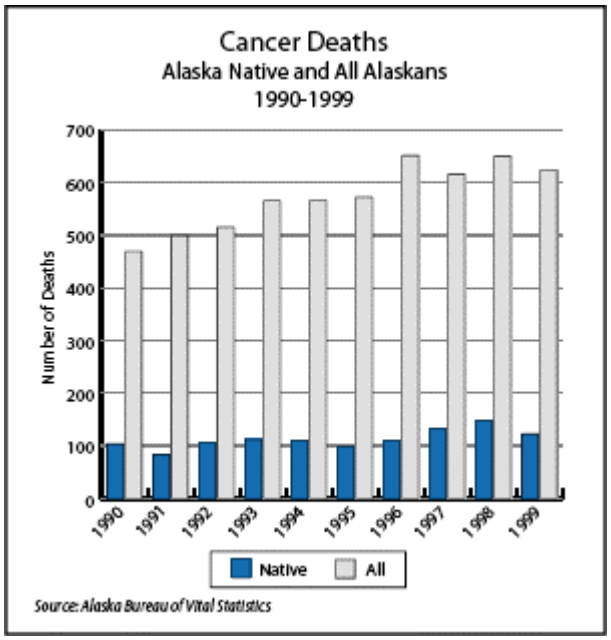

Fig. 12.1b

The American Cancer Society stated that 1 in 4 deaths in the United States are from cancer (American Cancer Society 2003). Table 12.1, provided by the American Cancer Society, shows the death rates due to cancer per 100,000 people in countries around the world. The Arctic Eight have different death rates that range from 241 (Sweden) to 328 (Denmark).

Table 12.1 Death rates for cancer in 45 countries around the world (per 100,000) (American Cancer Society)

Country	Male	Female	Total
Australia	150.9	103.2	254.1
Austria	168.6	113.8	282.4
Azerbaijan	114.2	61.8	176.0
Bulgaria	150.3	89.4	239.7
Canada*	160.5	116.7	277.2
Chile	141.2	108.7	249.9
China	143.3	76.9	220.2
Columbia	116.1	106.5	222.6
Croatia	230.1	105.4	335.5
Cuba	141.0	104.0	245.0
Czech Republic	222.2	127.6	349.8
Denmark*	184.9	144.0	328.9
Estonia	201.5	104.8	306.3
Finland*	145.8	92.5	238.3
France	201.5	98.0	299.5
Germany	176.6	116.9	293.5
Greece	149.5	81.8	231.3
Hungary	272.3	147.4	419.7
Ireland	170.2	127.8	298.0
Israel	135.1	111.4	246.5
Japan	159.5	83.1	242.6
Kazakhstan	201.9	102.6	304.5
Kyrgyzstan	185.6	112.6	298.2
Latvia	196.7	102.8	299.5
Lithuania	195.9	97.0	292.9
Macedonia	140.1	85.5	225.6
Mauritius	79.6	66.3	145.9
Mexico	112.5	106.3	218.8
Netherlands	182.0	120.0	302.0
New Zealand	167.2	131.1	298.3
Norway*	155.7	113.1	268.8
Poland	205.2	111.4	316.6

Portugal	157.1	89.1	246.2
Rep. of Moldova	157.8	89.4	247.2
Romania	150.0	90.0	240.0
Russian Fed.*	211.2	100.6	311.8
Slovakia	217.8	108.8	326.6
Slovenia	203.1	115.9	319.0
Spain	176.1	85.0	261.1
Sweden*	137.9	104.0	241.9
Trinidad & Tobago	103.5	101.9	205.4
Turkmenistan	117.7	85.2	202.9
United Kingdom	171.0	128.0	299.0
United States	161.8	116.4	278.2
Venezuela	104.1	91.8	195.9

Both basic research in animals and epidemiological studies have shown that one of the causes of cancer is environmental pollutants. The first evidence that cancer may be caused by some environmental pollutants can be seen as far back as 1879. In 1879, Härting and Hesse suggested the connection between an increased incidence of lung cancer and working in a radioactive-ore mine in Schneeberg, Saxony (Hueper 1955). Currently, it is believed that many cancer-related deaths are owing to environmental factors such as smoking, and chemicals in the air, food, and water, as well as radiation (American Cancer Society 2003). In this chapter, there will be a brief background on cancer and its mechanism, and then a discussion of the use of cancers and biomarkers.

Lecture

Cancer: Description and Mechanism

The mechanism of cancer is complex. Normal cells have the ability to multiply so that an organism can grow (i.e., develop to adulthood) as well as repair any injuries. Some cell types continue to divide throughout adult life, while others become quiescent. Cells only multiply when they are signalled to do so by a signal transduction pathway. However, in cancer cells, the pathway is modified so that inhibition signals are masked or ignored. An increase in cells in a tissue or organ is called hyperplasia. Neoplastic hyperplasia is owing to a hereditary change in a cell that gives rise to a chemically non-responsive daughter cell that ignores chemical signals to stop growth (Newman 1998). This uncontrolled growth in a cell line can give rise to a tumour. Differentiated or undifferentiated cells are classifications of cell types used to describe cancer. In a differentiated

cancer, the cells have not lost their structure and function as a normal cell, and they can be recognized. However, in an undifferentiated cancer, the cells have lost their morphology as well as the expression of certain proteins. New glycoproteins often appear on the cell's surface. In an undifferentiated cancer, these undifferentiated cells grow at fast rates and are not responsive to controlling molecular signals. Neoplasias that stay differentiated in morphology appear to have the functions of the differentiated cell type but grow slowly. They are called benign. Benign neoplasias do not invade other tissues. In dysplasia, cells appear abnormal in shape and orientation, but under a microscope they still look differentiated.

Malignant neoplasias, on the other hand, become undifferentiated, grow quite quickly, and invade other tissues. Cells of a malignant neoplasia can spread to another tissue type via the circulatory and/or the lymphatic system. In the new tissue, they form another tumour site and grow there. This is referred to as metastasis. Metastasis is what makes cancer so deadly. Normal cell movement throughout the body is controlled because cells are attached to other cells by cell-cell adhesion molecules or to the extracellular matrix. This is what keeps cells in the correct tissue type and at the proper number. If a cell is not attached to either another cell or the extracellular matrix, the cell most likely will die through apoptosis, that is, programmed cell death. Unlike normal cells, cancer cells do not undergo apoptosis and do not die when they become unattached. Thus, they can move throughout the body (Ruoslahti 1996).

If cancer remained in only the tissue of origin, the tumour could be removed by surgery and the patient condition would be improved. All of the cancerous cells need to be removed so that the tumour does not regrow. Chemotherapy or radiotherapy is used to destroy any remaining cells. However, some cancer cells, further mutated, can spread to other tissues before any clinical appearance of metastasis is detected. This is why it is so important to diagnose cancer as soon as possible, when localized in a single tissue.

There are two major classes of genes that play a role in the mechanism of cancer. The first of these is referred to as proto-oncogenes. These are genes that are inactive; but a proto-oncogene can be changed to an oncogene, a cancer-causing gene, by a variety of different carcinogens. Carcinogens are chemicals that may cause point mutations or other DNA rearrangements and gene insertions, all of which can contribute to the transformation of a proto-oncogene to an active oncogene (Newman 1998).

The second major class of genes involved in cancer is tumour suppressor genes. Two examples of tumour suppressor genes are the p53 gene and the breast cancer one (BRCA1 gene). Suppressor genes encode a signal transduction protein that supplies the growth-inhibiting message from one part of the cell to the nucleus. These genes inhibit the abnormal growth of cells. They work by either repairing damage in the cell or sending the cell into apoptosis. Thus, they

prevent the replication of defective cells. The major function of these genes is to inhibit the proliferation of abnormal cells; tumour-suppressor genes are the brakes of the cell. However, when mutations have occurred to these genes, the newly synthesized suppressor protein cannot function properly, and mutated cells begin to replicate. Mutations in tumour-suppressor genes have been detected in some human cancers, such as breast cancer.

There can be a long latent period between exposure to a carcinogenic agent and the clinical appearance of cancer (Newman 1998). After this long latent period, there is a period of cancer progression. The latency period is one reason that it can be so difficult to pinpoint the cause of cancer. Since a person is exposed to many toxins throughout his or her life, it is extremely difficult to determine which toxin may have caused the tumour. Also, the tumour may have been caused by a combination of toxins or radiation. To further complicate the identification, a person's genetic background—that is, his or her resistance or repair genes—can affect the development of a tumour after exposure.

Student Activity

1. What is the cancer rate in your community? How does it compare to your national average?

2. What do you think the major cause of cancer is in your community?

Biomarkers

In a scientific approach, it is difficult to develop a good hypothesis and obtain data that will lower the uncertainty of the results. It has been especially difficult to establish sufficient weight of evidence that a toxin is carcinogenic. Biomarkers are useful in reducing the uncertainty. Tumours and various cell qualities associated with gene products are used as biomarkers for environmental carcinogens. For example, two years after the Chernobyl release of radionuclides, the incidence of cervical cancer in Czech women increased (Newman 1998). The two years was the latent period, and the presence of the cervical cancer was used as the biomarker (see table 12.2).

Table 12.2 Types and definitions of biomarkers (Institute of Medicine 1999)

Type	Definition
Exposure	An exogenous substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism.
Susceptibility	An indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance.
Effect	A measurable biochemical, physiologic, or other alteration within an organism that, depending on the magnitude, can be recognized as an established or potential health impairment or disease

A major proportion of what is known about cancer processes that are associated with environmental contaminants (e.g., lead, mercury, cadmium, polycyclic aromatic hydrocarbons, organochlorides) came form epidemiologic research in the occupational health field. Unlike laboratory studies, these studies were observational in nature and not designed to understand mechanisms on a cellular and molecular level. One approach that can be used to access increased susceptibility is biomarkers. Biomarkers are measurements of the body's response to external events or substances, such as a carcinogen in the diet. A biomarker of susceptibility would measure limitations in a person's (or fetus's) ability to mount a protective response to a hazard (see table 12.2). The development of biomarkers allows analysis of differential susceptibility among minority or low-income populations.

In a study of anal cancer, which was conducted in Alaska (Wilt et al. 2002), researchers compared Alaska's average rate of colon cancer (cases per year) to the national average rate of colon cancer. They found that Alaska's average rate was similar to the national average rate. This study provides an example of a possible first step in researching cancer caused by an environmental toxin. If a higher incidence of colon cancer in Alaska was demonstrated, scientists may question whether the cancer was caused by a unique exposure in Alaska. Then they can set out to find the toxin, using the tumour as a biomarker.

In recent years there have been many attempts to find useful non-tumour biomarkers for cancer detection. Bladder cancer is the fifth most common cancer in the United States, with the main cause of death being metastasis. The relationship between bladder cancer and exposure to aromatic amines has been proposed for many years. A study was conducted to establish metallothionein isoform 3 (MT-3 protein) as a biomarker for human bladder cancer. Metallothioneins are proteins that bind metals and sequester them away from molecular sites of action. In the study by Sens et al. (2000), they used immunohistochemistry on normal bladder sections to identify the presence of

MT-3. They found that the immunoreactivity in the normal bladder was only nominally above background levels, which suggested that the normal human bladder does have a very low expression of MT-3. So the protein does exist in low levels in the normal bladder; this sensitivity is an important quality for a good biomarker. A good biomarker is expressed in normal tissues in order to provide a baseline prior to any contaminant exposure.

Next, the scientists looked for immunoreactivity in tumour sections of bladder cancer. For the tumour sections, all cases stained positive for the MT-3 protein, and the scientists found that the stronger the stain, the higher the tumour grade. Sens et al. (2000) summarized their results by stating that MT-3 is upregulated in human bladder cancer and the upregulation correlates with increasing tumour grade. Even though MT-3 would make a good biomarker, the mechanism of how MT-3 affects tumour growth needs to be developed because very little is known about MT-3 regulation at this time.

For an unbiased assessment of a hypothesis about chemicals and cancer, a framework relating to casual criteria is needed. The difficulty of developing criteria comes from (1) the number of studies conducted; (2) the improbability that a single study could provide all the necessary information to link an exposure scenario to a particular health outcome in wildlife or humans; and (3) the diverse circumstances (e.g., varied experimental conditions, numerous end points) from which data have been generated. It is important to recognize that the goal of this approach is not to provide point estimates of the association, but to reconcile different results from different studies. Also, because of scientific uncertainties, judgments may change as additional information became available.

A clear statement of the hypothesis under examination should contain two distinct elements. First, the outcome of concern (e.g., a specific cancer) is linked to a putative stressor that is acting on the individual or population. Second, exposure to the stressor results in events that ultimately result in the outcome of cancer. These elements should be clearly stated in order to evaluate the scientific evidence regarding their potential relationship. The evaluation of the evidence consider five aspects (see Darmstia et al. 2002):

1. The aspect of *temporality* explores whether the presumed cause of the outcome preceded the appearance of altered physiological states, rates of disease, or population health. Although information regarding the onset of exposure is often lacking, there are examples in which the temporal pattern of exposure precedes the observed effect.
2. The aspect of *strength of the association* examines (a) the incidence rate of the outcome in a population; (b) the extent to which other known risk factors may have contributed to this incidence; (c) the risk that could be attributed to the exposure of concern; and (d) the shape of the dose-

response curve as determined either from laboratory or population-based studies.

3. The aspect of *consistency of the observations* examines how frequently similar or dissimilar conclusions are reached in the literature. It also evaluates whether results came from multiple geographical areas, whether multiple species would be expected to react in a similar fashion, and whether studies employed similar dosages.
4. The aspect of *biological plausibility of the effect* examines multiple areas of research (e.g., basic aspects of biology, embryology, endocrinology, population dynamics, chemical/physical properties) that help determine the mechanism of action for the compounds of concern. Consideration of a substance's mechanism is critical because this criterion is central to the overall assessment of whether a substance is deemed to be a carcinogen.
5. The aspect of *evidence of recovery following diminution of the stressor* examines whether the occurrence of the adverse outcome is reversible upon diminishment or cessation of the suspected exposure. When examining the issue of recovery, it is important to note that some effects may be developmentally imprinted.

In research with cancer as a biomarker, we need consideration not only for humans but also for other species of wildlife and fish. In addition, the type of pollution as a causative agent must be considered on local, regional, and global scales (see fig. 12.2).

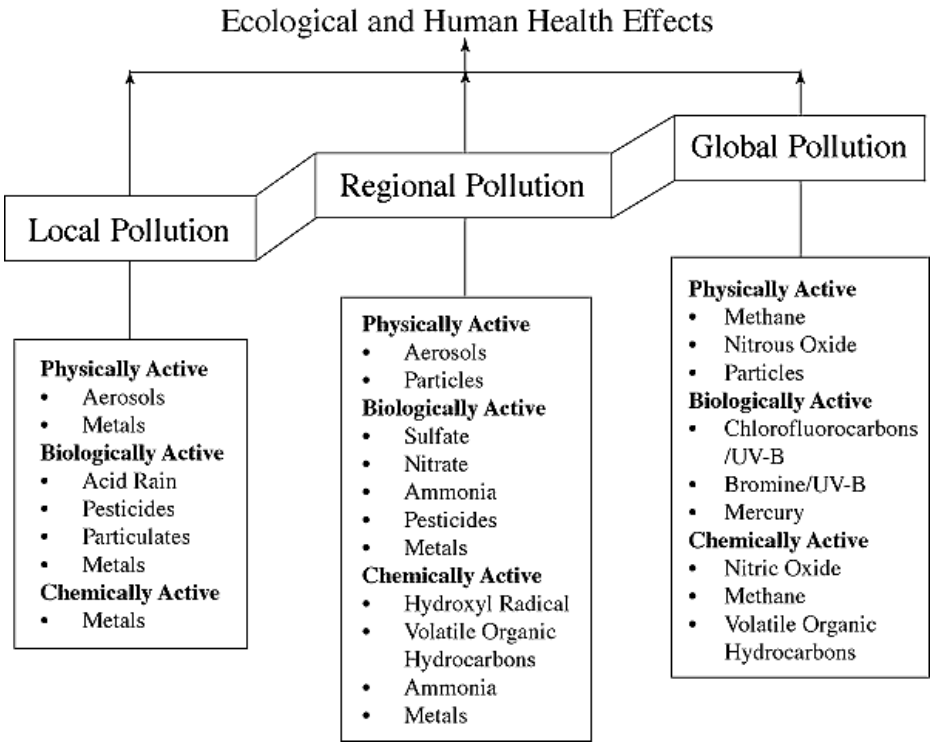

Fig. 12.2 Local, regional, and global distribution of pollution. Each panel shows the principle pollutant at the tree scales and whether the effects are owing to physical, biological (effects on human health, or ecological systems), and/or chemical processes (i.e., reactions in the atmosphere or water). Irrespective of the process affected by the pollutant, the ultimate concern is effects on ecological systems and human health.

Student Activity

Assume your community is concerned about the local cancer rate. Design a biomarker study to assess the potential exposure of residents.

Case Studies

Global Case Studies

By 1947, it was known that industrial workers had higher rates of lung cancer than agricultural workers (Hueper 1955; McCally 2002). The industry workers with the highest rate of lung cancer were exposed to chromium, nickel, or arsenicals. Table 12.3 shows environmental pollutants that, the weight of evidence suggests, can cause cancer when they are absorbed at an intensity and duration that exceeds the body's ability to expel the metal (Hueper 1955). Since

many of the occupational respiratory carcinogens occur as industry-related general atmospheric pollutants, these pollutants may cause a significant portion of lung cancers among members of the general population. Transboundary atmospheric pollution has been identified as an issue of concern for Arctic peoples (AMAP 2002).

Table 12.3 Recorded cases of cancer and toxin exposure (adapted from Hueper 1955)

Agent	Site of Cancer	Year Discovered	Number of recorded cases		
			United States	Other Countries	Total
Arsenic	Lung	1980	7	16	23
Asbestos		1934	22	74	96
Chromates		1932	75	65	140
Nickel		1932	0	84	84
	Nasal and nasal sinus	----------	0	51	51
Coal tar	Lung	1936	0	53	53
Petroleum oils	Lung and larynx	1936	7	33	40
Isopropyl oil	Lung	1946	1	0	1
	Larynx	----------	4	0	4
	Nasal sinus	----------	6	0	6
Radioactive Chemicals	Lung	1879	0	625	625
	Nasal sinus	1981	3	0	3
Total			**125**	**1,001**	**1,126**

One of the well-documented carcinogens is benzene (see table 12.4). Chronic exposure to benzene vapours has been linked to leukemia in susceptible individuals. Thus far, it is one of the few industrial chemicals definitely known to cause leukemia. Benzene causes acute myeloblastic leukemia and erythroleukemia in laboratory animals. The latent period has been shown to be from many months to several years. Benzene has been identified in the blood of exposed individuals and can reside in fatty body tissues for varying periods of time. Metabolic products of benzene have been identified in the urine of Alaskans (Isbell 2002), even with no industrial exposure. All peoples around the world are chronically exposed to benzene vapours through the air as a consequence of emissions from gasoline tanks, paint in houses, and cigarettes. In addition, people who work with benzene as a solvent are also exposed to high amounts of its vapours. Since the mechanism of benzene action is known, nutritional supplements may be useful in lowering benzene-related leukemia by interfering with its mechanism.

Table 12.4 Chemical carcinogens and target organs (American Cancer Society, http://www.cancer.org/cancerinfo)

Exposure	**Target Organs in Humans**
Arsenic	Lung, skin
Asbestos	Lung, pleura, peritoneum
Benzene	Hematopoietic system
Beryllium	Lung
Cadmium	Lung
Coal-tar pitches	Skin, lung, bladder
Mineral Oils	Skin
Nickel compounds	Nasal cavity, lung
Radon	Lung
Shale oils	Skin
Silica	Lung
DDT/DDE	Pancreatic
Soots	Skin, lung
Dioxin	Lung, soft-tissue sarcoma
Tobacco smoke	Lung, bladder, oral cavity, pharynx, larynx, esophagus

In the northern hemisphere, an increase in cancers at hormonally sensitive sites—such as the breast, uterus, prostate, and testis—are being linked to exposure to endocrine-disrupting chemicals, or EDCs (Darmstia et al. 2002). Laboratory studies have shown that these types of cancers are dependent on or modulated by hormones or their cellular receptors. It has been hypothesized that compounds containing chlorine and ring-shaped components mimic the body's estrogens (endogenous), and thus stimulate cell division in the body's reproductive organs (Trichopoulos et al. 1996). These types of compounds are known as xenoestrogens. Increases in cancer (see table 12.5) appear to roughly correspond to the increase in release of chemicals associated with food and atmospheric exposure (Godduhn and Duffy 2003; McCally 2002).

Table 12.5 Trends in US cancer incidence and mortality 1973–1998 (adapted from McCally 2002)

Decreasing Incidence and Mortality	Increasing Incidence and Mortality
Oral cavity and pharynx	Esophagus
Stomach	Liver and intrahepatic bile ducts
Colon and rectum	Lung and bronchus
Pancreas	Melanomas of skin
Larynx	Prostate
Cervix uteri	Kidney
Corpus and uterus, not otherwise specified	Brain and other nervous system
Hodgkin's disease	Non-Hodgkin's lymphoma
Leukemias	Breast

More specifically, since the 1940s breast cancer has increased steadily in many industrialized countries. Some of these cancers may be related to the modern lifestyle, such as the widespread use of hormonal contraceptives or hormone replacement therapy. Still, others may be related to environmental exposures to EDCs such as persistent organic pollutants (POPs) that can be found in both pesticides and insulating oils. Although there has been a lot of controversial data on the effects of POPs, there seems to be a relationship between an increase in cancer and the increase in the increasing number of industrial chemicals in the environment (Davis 2002).

Dichlorodiphenyltrichloroethane (DDT) is an agricultural pesticide that was banned in the United States in 1973 and is included in the Stockholm Convention. DDT and its metabolite, dichlorodiphenylethane (DDE), are known to bioaccumulate in the human body. The half-life in plasma of *p, p'*-DDE is about 10 years. DDE and dichlorodiphenyldichloroethylene (DDD) are derivatives of DDT. Laboratory studies have shown a positive dose-related response between DDT and pancreatic cancer; Cocco et al. (2000) found that White men and women had increased levels of mortality from liver cancer with increasing amounts of adipose DDE. They did not find that same relationship in African American men or women. There have been several other studies on DDT and increased cancer incidents. Since some show a relationship to cancer and others do not, it was hard to prove whether or not DDT was a carcinogen until the molecular mechanism was identified. Since scientists have used mortality rates rather than incidence rates (Cocco et al. 2000), studies that use incidence rates may be slightly skewed lower because some people die of other causes before the cancer is detected. Another epidemiological problem is the assumption that the entire population of a given area has the same level of exposure to a contaminant. This is referred to as the "ecological fallacy" (Cocco et al. 2000).

The US Centers for Disease Control and Prevention have pointed out that, if all socio-economic factors were equal, one might expect the concentration of environmental chemicals to be evenly distributed across a US population that is approximately three-quarters White and one-quarter people of colour. However, they found a distribution that is most closely paralleled to the naturally occurring environmental chemicals (metals; phytoestrogens; and polycyclic aromatic hydrocarbons, or PAHs) that people touch, eat, or breathe in (see table 12.6). Nevertheless, synthetic chemicals that people touch, eat, or breathe in (such as dioxins, PCBs, phthalates, pesticides, herbicides, pest repellents, and disinfectants) can pose a greater burden to economic minorities.

Table 12.6 Environmental exposures and racial disparities in the United States (Center for Disease Control and Prevention)

Mexican-American	Pesticides: 26 chemicals examined. 6 of the 26 are not found in any person. Of the remaining 20, 6 are widely found. The mean level of 2 of the 6 is highest in Mexican-Americans while the mean level of the remaining 4 is highest in non-Hispanic Whites. Of the 14 that are not widely found, the highest levels of 7 are in Mexican-Americans.
	Herbicides, Pest Repellents and Disinfectants: 9 chemicals examined. 4 of the 9 are not found in any person. Of the remaining 5, 3 are widely found and had a mean level highest in Mexican-Americans. The 2 that are not widely found are detected in highest levels in non-Hispanic Blacks.
	Limited exposure: The polycyclic aromatic hydrocarbon, Chrysene, is only detected in Mexican-Americans.
Non-Hispanic Blacks	PCBs and Dioxins: 40 chemicals examined. 21 of the 40 are not found in any person. The remaining 19 are not widely found. The highest levels of 18 of the 19 are in non-Hispanic Blacks.
	Phthalates: 7 chemicals measured. Of the 7, 4 are widely found. The mean level of 3 of the 4 widely found is highest in non-Hispanic Blacks. The highest levels of the 3 that are not widely found are detected in non-Hispanic Whites.
	Tobacco smoke: 1 chemical measured. It is not widely found and is detected in highest levels in non-Hispanic Blacks.
	Limited exposure: 5 chemicals (3 types of dioxins and PCBs, the pesticide Mirex, and the herbicide 2, 4-Dichlorophenoxyacetic acid) are only detected in non-Hispanic Blacks.
Non-Hispanic Whites	Metal: 13 chemicals examined. 2 of the 13 are not detected. The remaining 11 are widely found. The mean level of 7 of the 11 is higher in non-Hispanic Whites. The highest levels for 6 of the 11 are in non-Hispanic Whites.
	PAHs: 14 chemicals examined. 2 of the 14 are not detected. Of the 7 that are widely found, the mean level in non-Hispanic Whites is higher in 5. The highest levels for 6 of the 12 that are detected are found in non-Hispanic Whites.
	Phytoestrogens: 6 chemicals examined. The mean level in non-Hispanic Whites is higher in 5 of the 6. The highest level for 4 of the 6 is in non-Hispanic Whites.
	Limited Exposure: There were no chemicals that are found only in non-Hispanic Whites.

Also, it should be noted that the health of children under five, including cancer incidence, can be damaged by a poor-quality environment for several reasons:

- Young children have a greater exposure to environmental toxins than adults.
- Metabolic pathways are immature.
- Rapid growth and developmental processes are easily disrupted.
- Early exposures can trigger chronic effects.
- Effects may not be apparent until adulthood.

Poor-quality environments are associated with poverty, which is a major predictor of poor health. This is because poor children are least able to

- obtain uncontaminated water and food.
- receive immunizations.
- receive quality health care.
- have access to information.

Brain cancer increases are among the new areas of pediatric morbidity. For example, the exposure to mercury and pesticides are an enormous threat because the effects of these individual contaminants may be synergistic. *The Bangkok Statement*, signed in 2002 during the International Conference on Environmental Threats to the Health of Children, in Bangkok, stated that "all children should have the right to safe, clean and supportive environments that ensure their survival, growth, development, healthy life and well-being" (WHO 2002).

Because of the rise in breast cancer, the effect of organochlorine compounds in an in vitro cell culture system with a breast cancer cell line, MCF-7, was used to monitor cell proliferation. MCF-7 is an adherent, epithelial cell line that retains the ability to process estradiol via cytoplasmic estrogen receptors (ATCC, http://www.ATCC.org). Four different organochlorine compounds were studied: 1-(o-chlorophenyl)-1-(p-chlorophenyl)-2,2,2-trichloroethane (o,*p'*-DDT), 1,1-bis-(p-chlorophenyl)-2,2,2-trichloroethane (*p,p'*-DDT), which are estrogen receptor agonists, and β-hexachlorocyclohexane (β-HCH), 2,2-bis-(p-chlorophenyl)-1,1-dichloroethylene (*p, p'*-DDE) which stimulate cell division. Each one of these organochlorine compounds alone induced cell proliferation during these experiments. A synergistic effect was seen with respect to the more potent compounds o*, p'*-DDT and *p, p'*-DDE. When the four compounds were mixed in equal amounts, they produced a significant amount of cell proliferation even when the amounts of the individual compounds were below the NOEC (no observed effect concentration) level (Payne et al. 2001). This data supports the idea that these organochlorines in combination at low concentrations have the potential to be carcinogenic.

These experiments also point out that testing of one contaminant alone does not always provide a true explanation of what is actually happening between human bodies and environment. The scientific establishment is now accepting the idea that mixtures of chemicals have emergent effects. Concentrating on one contaminant at a time may provide us with a misconception of little effect from a particular toxin, and a false notion that a particular compound is not carcinogenic. These concepts are extremely important because humans are most likely exposed to many contaminants simultaneously because of their worldwide distribution (Davis 2002).

Arctic Case Studies

There has been an increase in Non-Hodgkin's Lymphoma (NHL) over the last two to three decades. Hairy cell leukemia, a B-cell malignant lymphoma, is a subgroup of NHL. One of the increased risks for NHL is exposure to any type of immunosuppressant chemical such as polychlorinated biphenyls (PCBs). PCBs are chemically stable compounds in that the half-life of PCBs in the human body ranges between 7 and 30 years. It has been observed that PCBs cause measurable changes to the immune system. A dose-response relationship has been established between lipid-corrected blood concentrations of total PCBs and the risk for NHL in a Swedish population (Nordström et al. 2000). It appears that the PCBs are suppressing the human immune system, thus making people more susceptible to NHL. This may be one cause of an increase in NHL over the last few decades.

The Epstein-Barr virus (EBV), a human herpes virus, has also been associated with hairy cell leukemia. Elevated antibodies to the Epstein-Barr early antigen and the viral capsid antigen are often found in people with hairy cell leukemia. Nordström et al. (2000) found a correlation between an increased titre to Epstein-Barr early antigen and increased risk to hairy cell leukemia. This risk increased when the concentrations of organochlorines in the individual increased. The interaction between EBV and immunosuppressors such as PCBs, thus, led to a higher risk of hairy cell leukemia in exposed humans. Their findings "suggest the possibility of EBV and organochlorines acting as component causes in the pathogenesis of hairy cell leukemia" (Nordström et al. 2000).

In contrast to industrial Sweden, Alaskans who hunt, fish, and gather their own food are finding that subsistence foods are contaminated with low levels of persistent organic pollutants (POPs). POPs may be both carcinogenic as well as teratogenic, that is, cause developmental malformations. One of the major routes of exposure to POPs for people living in the Arctic and Subarctic is through their diets, which include large amounts of fish. These chemicals are bioamplified up the food web; that is, they are increased from one tropic level to the next. They are also very persistent because of their lipid solubility and slow elimination (Klopov 1996; Godduhn and Duffy 2003). Another major route of

exposure is through the transport of POPs from lower-latitude industrialized areas of the world to the Arctic. Thus, Arctic people are being exposed to POPs that are not even used in the Arctic (Godduhn and Duffy 2003). High levels of POPs were found in cord blood and placenta of people living in the Russian Arctic (Klopov 1996; Middaugh 2003).

A study on contaminants in northern Quebec confirmed that both fish and marine mammals have levels of polychlorinated biphenyls (PCBs) that exceed the Canadian guidelines. This would explain why the people living in these areas and eating marine life would have high levels of PCBs in their blood and in cord blood. Researchers in Barrow, Alaska, have made similar observations.

Another cause of cancer may be the loss of ozone, which is leading to the increase in ultraviolet radiation over the polar regions of the Arctic. The ozone in the northern polar regions has decreased by about 10% from 1970 to 1990 (Kolstad 1996). UV-B (260–300 nm) can cause damage to many biomolecules, such as DNA. Skin acts as a barrier between the UV-B and biomolecules to reduce the incidence of DNA mutations. However, skin cancer in the North can be a problem because UV can suppress the immune system and this suppression leads to a decrease in the body's ability to recognize cancer cells and induce apoptosis. Since a correlation has been found between sunburns and melanoma, skin cancers are of concern, given the increased UV-B. The incidence of skin cancer in the Subarctic areas is rising; however, the incidence of skin cancer in High Arctic areas does not seem to be rising at this time (Kolstad 1996). Although skin cancer does not appear to be a serious problem now, it will require constant monitoring in the future.

Another type of cancer-causing radiation is ionizing radiation, that is, nuclear radiation. The Chernobyl nuclear plant accident in Ukraine, which released radioactive isotopes, has had a major impact on the people in Belarus, Ukraine, and Arctic countries. In April 1986, one of the reactors of the Chernobyl nuclear plant released about 190 tons of radioactive uranium, iodine, and carbon into the atmosphere. The fallout from this explosion exposed people to radioactivity 90 times greater than the radioactivity that was released by the atomic bomb dropped on Hiroshima in 1941. More than half of the radioactivity fell on the country of Belarus. Although about 2,000 towns in Belarus were evacuated shortly after the explosion, many of these people were adversely affected by the fallout. The number of new thyroid cancer cases in Belarus after 1986 increased by about 3.9-fold over the previous rate of new thyroid cancer cases. Shortly after the accident, it became evident that the iodine isotopes that were released increased the thyroid doses of iodine in children (Ilyin et al. 1990). It was hypothesized at that time that the increased dose would have adverse effects on the thyroids of these children in the future. Years after the incident, that hypothesis has been supported by reports that there was an excess risk for thyroid cancer of 2.21 for girls and 1.62 for boys (Ivanov et al. 1999). A linear relationship between the dose and the risk was observed as well as a dependence

of risk with age at exposure time. There was a risk of 14 times higher in children less than 4 years of age than in adults. In this case, a link between the radioactive iodine isotopes and an increase in thyroid cancer was clearly established. There are many nuclear test sites and storage areas in the Arctic and Subarctic regions that pose a possible hazard of increased cancer in local populations, especially in southern Siberia. Amchitka, in Alaska, is an issue of concern for Aleuts who depend on fish and marine mammals.

Since cancer is a complex disease, a large variety of factors can contribute to cancer, including exposure to environmental toxins, like POPs. The complexity is only enhanced when individuals, lifestyles, and genetic backgrounds are taken into consideration. The synergistic effects of carcinogens also complicate the issue. Knowing that there is even a possibility that a compound could be carcinogenic should motivate leaders to increase the amount of research done on new chemicals before they are released into general distribution. Although this will increase the amount of time and money required to mass-produce new compounds, it will be worth it for future generations.

Indoor Air Pollution and Cancer

Benzene and toluene are two indoor air pollutants of concern in Arctic homes with attached garages (Isbell et al. 2002). In particular, the homes in Alaska are generally designed and built for maximum airtight construction to minimize heat loss and associated costs during the long and cold winter months. Many homes have attached garages, inside which vehicles are parked; fuel is stored in containers, and a variety of other fuel containing small engines such as snowmobiles, motorcycles, lawnmowers, and chainsaws are also present. People spend a large amount of time at home in their living areas during the many months of winter, maximizing their exposure to these compounds. The outside air quality in the Arctic can be poor in the winter, and violations of the US National Ambient Air Quality Standards (NAAQS) can occur, with vehicle emissions cited as the major causative factor. Pollutants from these emissions tend to be “trapped” low to the ground by low atmospheric inversions; when coupled with poor dispersion conditions (i.e., low winds), the result is an accumulation of pollutants.

The benzene and toluene levels inside homes with attached garages were measured in summer in Fairbanks, Alaska. The range of benzene and toluene found in homes was 0.1–111 ppbv. A correlation between toluene and benzene levels suggested the same point source. The benzene and toluene content of the indoor air and the number of small engines stored in the attached garage was also correlated. This study calls attention to the role of small engines as a source of indoor air pollutants, such as benzene and toluene. Large numbers of these engines, whose tank seals are not regulated, may increase the risk of benzene exposure to rural northern residents. In rural areas, the frequency of these types

of small engines is higher than in more urban areas, but there is a continued increase in all areas of the Arctic.

Studies such as this show surprisingly high levels of benzene and toluene in homes with attached garages. However, there is a lack of correlation between the indoor air levels of benzene and toluene and their respective biomarkers. Urinary concentration of t,t-MA reported among people with no occupational exposures ranges between 0.037 and 0.22 mg/g creatinine (Dor et al. 1999). In Alaska, t,t-MA levels were higher: 0.10 to 0.86 mg/g giving a mean of .35 mg/g creatinine (Isbell 2002). Although this mean is higher than the mean Dor et al. (1999) reported for unexposed populations, it is lower than levels reported for exposed urban populations at lower latitudes, which range from 1mg/g creatinine to as high as 20. Individuals can differ by factor of 5 or more, and researchers have reported a bimodal distribution representing efficient benzene metabolizers and poor metabolizers. This is an example of the new field of toxicogenomics. Inter-individual variability would limit finding correlations in small population studies in Arctic villages.

Additional factors affecting biomarker variation are diet, exercise, exposure levels, and time spent inside homes. Research indicates that these biomarkers are too variable at these non-occupational exposure levels where the contribution of dietary sources of sorbitol and benzoic acid become significant sources of metabolites in the urine. Sorbitol, which is common in food, forms the t,t-MA biomarker during normal metabolism. The exercise level and the time spent in the homes also vary between individuals. In future studies of non-occupationally exposed individuals, diet type, daily exercise level, and time spent indoors must be noted.

Gasoline, Additives, and Carcinogenicity

The intentional sniffing of high concentrations of gasoline vapours has an established acute symptimology that includes eye irritation, dizziness, excitement, intoxication, nausea, anesthesia, muscular weakness, and liver and kidney damage. Death has occurred from exposure to vapours for 5 minutes at 5,000 ppm. Health effects studies on long-term occupational inhalation of gasoline vapours have suggested serious health effects such as cancer. In laboratory animals, the primary toxicological effects of short-term exposure are central nervous system depression and kidney disease. These effects are dependent upon age and type of exposure. In human cases, depression of the central nervous system occurs, as well as an irritation of the mucous membrane.

Studies of employees in the petroleum refinery industry suggest that the risk of cancer is probable and should be a major concern. Based on total available evidence, gasoline is classified as a Class 1A human carcinogen. Currently, the US Environmental Protection Agency (EPA) classifies gasoline as a probable human carcinogen; however, the US EPA Risk Assessment Forum concluded

that “the association between human kidney cancer and exposure to petroleum distillates, if there is one, does not suggest high risks for the types of exposures that have occurred in the past.” The hazard to human health is potentially high because of the high volatility of gasoline and the rapid rate at which harmful concentrations may develop in a non-ventilated area. Inhalation is the most common route of occupational exposure.

Investigations into gasoline toxicology were conducted by the American Petroleum Institute (API) in the mid- to late 1980s. Chronic inhalation experiments using wholly vaporized unleaded gasoline resulted in significant depression in the body weight gain of rats and mice at high concentrations (2,060 ppm). The other consistent exposure-related changes were the occurrence of adenomas and carcinomas in male rats’ kidneys. The tumours appeared to be dose-related and did not exhibit metastasis. A significant increase in hepatocellular tumours was seen in female mice as well. Benzene, toluene, and xylenes are classified as proven human carcinogens and teratogens, while 1, 3-butadiene and formaldehyde are classified as probable human carcinogens. Non-cancer effects from acute exposure to formaldehyde have also been reported.

MTBE is a gasoline additive that is eliminated by either exhalation or metabolism. When inhaled by humans, approximately 32%–42% is rapidly absorbed into the blood and distributed throughout the tissues. Metabolism of MTBE occurs primarily in the liver and to a lesser extent in the upper respiratory tract. A major proportion of MTBE has a half-life in blood of up to 1.5 hours, while some of the MTBE lasts much longer, with a half-life of 20 hours, indicating possible partitioning of MTBE into particular tissues or bound to blood components. In general, 95% of the MTBE will have been eliminated within 48 hours. Figure 12.3 represents the metabolic pathway of MTBE. The first step is oxidative demethylation by cytochrome P450 enzymes to yield formaldehyde and tertiary-butyl alcohol (TBA). Formaldehyde is rapidly metabolized to formic acid.

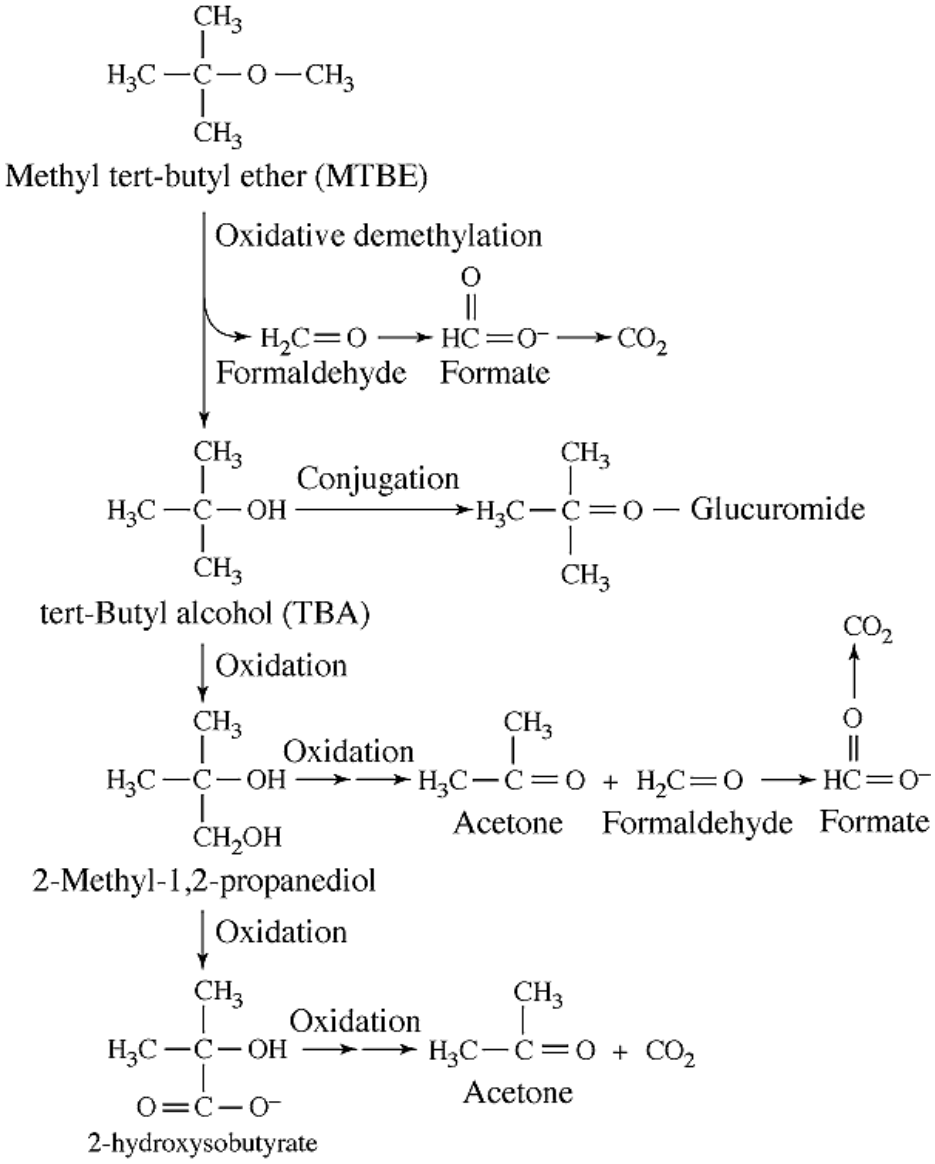

Fig. 12.3 Possible metabolic pathways of MTBE

Evidence for carcinogenicity of MTBE appeared to be marginal, but some carcinogenic effects have recently been reported on rats administered MTBE. Since cancer can be related to a suppressed immune system, MTBE was also studied for its effects on cytokines. After the introduction of oxyfuels to Alaska, residents reported symptoms that included headaches, nausea, and throat and eye irritation. These symptoms are similar to those associated with formaldehyde toxicity. Tests on mice showed a slight increase in natural killer cell-mediated cytotoxicity and in rats showed increased counts of white blood cells.

Cytokines are a group of proteins of low molecular weight (usually <20 Kd) used by immune and injured cells to communicate with each other. They take part in all phases of injury, including inflammation, immune response, hemopoiesis, and repair of tissue. Cytokines are produced at a site of injury or stimulation and act locally in a paracine or autocrine fashion. They may also circulate and have hormonal-like effects—acting at sites distant from the original site of secretion.

The hypothesis underlying studies on MTBE was that cellular injury owing to MTBE exposure will result in the local generation of cytokines and that these may leak into the blood stream. Such factors could be used as biomarkers of lung injury.

In one study, IL-1, which was measured in 10 subjects, was below the detectable limits of the assay, 10 pg/ml. However, IL-6 levels were detected in all but two of the morning samples and five of the evening samples. There was no difference between the morning mean levels of IL-6 (2.50 ± 2.4 S.D.) and the evening mean levels (2.53 ± 2.6 S.D.). Fourteen out of 22 samples showed some increase of IL-6 during the day. Future studies on cytokines are needed in the Arctic.

Over the past 25 years, the list of established human carcinogens in the Arctic has grown substantially. This is owing, in part, to the accumulation of knowledge about the human health effects of various chemicals, drugs, and metal exposures during this period. Transboundary exposure to chemicals is of particular concern because of the size of the population that may be exposed in the Arctic.

A group of authors at the Harvard Center for Cancer Prevention suggested that 30% of total cancer deaths were attributable to tobacco and another 30% were attributable to adult diet/obesity. They estimate that 5% of cancer deaths are attributable to occupational factors, 2% to environmental pollution, and the remainder to a variety of other factors. The accuracy of these estimates is open to question, but it is not productive to play once cancer cause against another (McCally 2002). Some factors interact and magnify the effect of each acting separately. The usual recommendations for cancer prevention, such as those offered by the American Cancer Society, include smoking cessation, eating a diet low in meat and dairy products, increasing physical activity, and getting periodic checkups and screening tests. While these are rational recommendations, they are necessarily general and not focused on particular circumstances about which exposed community residents may be concerned.

Epigenetics

It is important to note that a genome's context, not just the code in a gene, plays a vital role in development. Recently, in cancer research, an entirely gene-centered view of a linear path of disease development has been predominant. This view can be summarized this way: "A particular genetic endowment leads to a particular attribute in the organism." In fact, however, the beginning of an organism's development may be more similar to the firing of a pinball machine. It has been observed that environmental manipulations can produce phenotypic variations. These variations cannot be passed on through the genes, but the environmental context can induce the expression of an alternative phenotype—the potential for which is already encoded in the genome. For example, nutritional differences can produce different phenotypes in bees.

This ability to change and vary is called plasticity. Plasticity is studied on a molecular and cellular level in biochemistry and neuroscience. Although the genes must be present, we can exhibit induced developmental plasticity. For example, our immune systems adapt to the bacteria it is exposed to. Mothers have the capacity to pass on common immunity to their babies using their IgG antibodies via the placenta. Our lymphocytes' behaviours depend on both experience and genes.

Lastly, just as in the development of a neuron or an immune cell, an organism or population will depend on both experience and genes in their development and behaviour. The development of ideas should also be understood within the context of their social environment. Human society develops in a context influenced by religion, politics, economics, and even gender. Our attitudes towardsdisease and cancer will change as the context—that is, knowledge—improves.

Student Activity

1. Are any research studies related to cancer being conducted in your community? Does the community support these types of studies?

2. Is there concern in your community about radiation exposure and cancer?

Summary

Cancer can be initiated by chemicals that cause mutations. About 5% of all cancers are caused by chemicals. Other causes include radiation, viruses, chronic trauma, aging, and genetic predisposition. There are certain genes in cell nuclei known as proto-oncogenes. When the cell is damaged in a special way, these genes are converted to oncogenes. The process in which the affected cell evolves into a tumour is a series of separate events. The first stage is the formation of an abnormal cell that does not proliferate (initiation). In the second stage, promotion occurs months or years later. In a later stage, malignant cancers can invade other tissues.

Everyone is at risk of cancer. Cancer may strike at any age. Although there are certain specific childhood cancers that have an expected early age peak and are then rarely seen in the rest of the population, the occurrence of cancer generally increases with age and the majority of cancers occur among adults middle-aged or older.

Breast cancer rates have increased, and research studies have helped related genetics, hormones, and chemical exposures demonstrating a complex interaction between many factors.

Many breast cancer risk factors, such as age, family history of breast cancer, reproductive history, previous breast disease, race and ethnicity, are not subject to intervention. However, being overweight is a well-established breast cancer risk for post-menopausal women that can be addressed. Avoiding weight gain is one method by which older women may reduce their risk of developing cancer.

Case studies are the best way to understand complex processes, such as cancer.

Study Questions

1. List two causes of cancer.
2. What is the difference between a mutagen and carcinogen?
3. What is meant by the statement that carcinogenesis is a two-step process?
4. What is the difference between a benign tumour and a malignant tumour?
5. Can lifestyle cause cancer? Explain.
6. Why is radioactivity used to treat cancer?
7. Outline the sequence of events that lead to the formation of a tumour.

8. What is a procarcinogen?

9. List the different classes of biomarkers.

10. What is a good biomarker for indoor air pollution from gasoline?

Glossary of Terms

agonist	a molecule that has the same biological effect as the natural gland for a receptor.
apoptosis	a programmed process of molecular events leading to cell death.
B-cell	a cellular component of the immune system that produces antibodies.
benzene	a six-member carbon ring with conjugated double bonds.
biological half-life	the time required for the amount of contaminant to decrease by 50% in a tissue.
biomarker	a cellular, tissue, body fluid, or biochemical change that is used to quantitatively imply the presence of a pollutant or indicate an early warning of an adverse health effect.
cancer progression	the change in the attributes of neoplastic cells over time that leads to malignancy.
capsid	the protein coat or shell of a virus.
carcinogen	any substance that is capable of causing cancer.
clastogenic	capable of causing chromosome damage in living cells.
compensatory hyperplasia	an excessive amount of hyperplasia occurring in response to injury or chemical irritation.
congeners	a term used to point out the relationship among members of a chemical family, such as PCBs.
contaminant	a substance released by human activities that causes impurity by contact or mixture; a pollutant.
cytotoxicity	toxicity causing cell death.
DDT	a chemical pesticide of the organochlorine class.
effective dose (concentration)	a term used in pharmacology and toxicology to define the amount of drug or toxin that has a defined activity.
epidemiology	the science concerned with the cause, incidence, prevalence, and distribution of diseases in populations.

etiological agent	a chemical or agent responsible for causing or promoting a disease.
estrogenic chemicals	contaminants that cause changes in sexual characteristics or function of individuals.
exposure	contact with the contaminant or stressor.
glycoprotein	a protein with many sugar residues attached.
hormonal oncogenesis	tumour production resulting from high levels of hormones that act as promoters; usually associated with hyperplasia.
hyperplasia	the capacity of cells to multiply and increase in tissues and organs.
in vitro	(of processes or reactions) performed, obtained, or occurring in a test tube, culture dish, or elsewhere outside a living organism.
in vivo	(of processes) taking place in a living organism.
incidence	the number of new individuals scored as having the disease or cancer in a time interval.
incidence rate	the number of individuals with cancer divided by the total time the population is exposed; usually expressed as cases per time.
initiator	an agent producing cancer by converting normal cells to latent tumour cells.
latency (period)	the time or lag between exposure to a carcinogenic agent and the appearance of cancer.
lesion	alterations in cells or tissues indicating exposure or damage.
ligand	a molecule that forms a coordination compound or complex with a receptor or a metal.
malignant neoplasia	a cellular hyperplasia with the ability to spread to other tissues.
metastasis	the process in which parts of a cancerous growth dislodge and move to other tissues via the circulatory or lymphatic system to establish new tumour sites; this process leads to the spread of cancer.
mutagen	a chemical capable of producing mutations.
neoplasia	hyperplasia caused in part by an intrinsic heritable abnormality in the cells; results in cancerous growth.
neoplastic hyperplasia	hyperplasia resulting from a hereditable change in a cell such that it no longer responds properly to molecular signals that control cell growth.

NOEC	no observed effect concentration (level); this is the highest concentration in a test for which there was no statistically significant difference in response from that of the control or reference.
oncogene	a gene that can transform a cell into a tumour cell.
PCB	polychlorinated biphenyl; any of several toxic aromatic compounds containing two benzene molecules in which hydrogens have been replaced by chlorine atoms; formed as waste in industrial processes.
POPs	persistent organic pollutants; pollutants that are long-lived in the environment and tend to increase in concentration as they move through food chains.
pollutant	a chemical that occurs in the environment as a result of human activity; has an adverse effect on living organisms.
procarcinogen	a compound that is converted to a carcinogen.
promoter	an agent producing cancer by enhancing the growth of mutated cells.
proto-oncogene	a gene involved in normal growth which, upon mutation, becomes an oncogene.
suppressor gene	a gene that functions normally to suppress cell growth and may inhibit abnormal growth.
synergism	the sum of the toxic effects of a mixture is greater than the additive effect.
tumour	a cancerous growth.
weight of evidence	the available evidence convinces a reasonable person that the conclusion is plausible. The more the evidence supports the conclusion, the stronger the "weight of evidence."
xenobiotic	"foreign" chemical not produced in nature or considered to have a biological function.

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