chapter 17:

CANCER

OBJECTIVES

After studying this chapter you should be able to:

- explain what is meant by the following terms: cancer, malignant, neoplasm, tumor;
- discuss the incidence and epidemiology of cancer;
- describe and explain some of the environmental causes of cancer;
- outline the relationship between gene mutations and cancer;
- describe how cancer may be clinically detected;
- describe the clinical features of some cancers;
- explain how cancers may be treated.

17.1 INTRODUCTION

In multicellular organisms, the growth of cells by division is under tight control (*Chapter 15*). Cells divide when stimulated with the requisite internal and external signals (*Figure 17.1*). This strict control of cell division ensures that division occurs at a rate appropriate to the structure of the tissue or organ. In some tissues, for example bone marrow, skin and gastrointestinal (GIT) endothelium, cells divide constantly, replacing ones that have died. However, in other tissues, such as nervous tissue, mitosis is rare and lost cells are not replaced. In yet other tissues, cells can commence dividing when required as, for example, in the regeneration of liver or during the healing of wounds in the skin. The term **cancer** covers a number of diseases in which the growth of cells becomes uncontrolled. Cancer cells fail to respond to the usual controling signals and their growth becomes unregulated. Indeed, the name *cancer* comes from a Latin word meaning 'a crab', and describes the manner in which the pattern of penetration into normal tissues by the abnormal growth bears a superficial resemblance to a crab's claw. These abnormal cells may

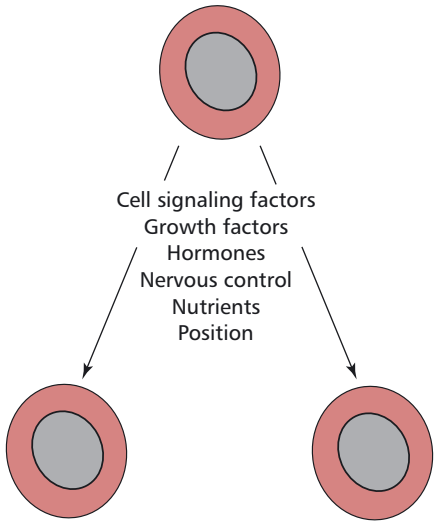


Figure 17.1 Some intrinsic and extrinsic factors that influence cell division.

invade nearby tissues and may enter the blood and lymph systems and spread to remoter areas.

Today, the term cancer is used popularly to describe what is known as a **malignant tumor**. **Oncology**, derived from the Greek word *oncos*, a lump, is the branch of medicine involved with the study of the development of tumors, their epidemiology, diagnosis and treatment. A tumor is an abnormal mass of cells that may be benign or malignant. Benign tumors generally grow slowly and do not spread to other tissues, though they may continue to grow *in situ*. Such tumors are only harmful if they interfere with the normal function of a tissue, or if they cause pressure by growing within a confined space, such as in the brain. A malignant tumor is one that spreads from its initial site, where it is known as the **primary** tumor, through the blood and lymph to establish **secondary** tumors in other organs. Such movement from the primary tumor and the formation of secondary tumors is known as **metastasis**. A term that is often used in the context of cancer is **neoplasm**. This means, literally, a new tumor or new mass, but is generally used to describe a cancer.

The causes of cancer are complex and varied. Some arise from environmental agents called **carcinogens**, others are brought about by oncogenic, that is cancer-inducing, viruses. Most cancers arise, ultimately, from mutations in DNA. These mutations may be caused by environmental agents, or may be inherited in the germ line, making individuals more susceptible to cancer.

Margin Note 17.1 The germ line

Germline DNA refers to the DNA which is present in the cells that give rise to the gametes, that is, the sperm and eggs (*Chapter 7*). The egg and sperm fuse to form a zygote, and, as further divisions occur, that DNA is passed to all the cells in the developing embryo. Mutations which occur in germline DNA are present in the gametes and in all the cells of the individuals to which they give rise.

Cancers can arise from any tissue in the body; indeed, they have been detected in over 200 different sites. Some sites are more susceptible than others, the commonest being the lungs, breasts, prostate, GIT and skin. While most cancers occur more frequently in the old than in the young, with cancer generally being regarded as a disease of aging (*Chapter 18*), certain cancers occur typically in children. In the UK it has been estimated that one in three individuals will develop a cancer at some time in their life and that cancer causes one in four deaths. Treatment of cancer represents 6% of all NHS hospital expenditure. Similar incidence rates are seen in the USA.

This chapter will review the biology of cancer and its consequences to the individual. The causes of cancer, including genetic aspects, environmental insults and viruses will be examined. The involvement of the pathology laboratory in the screening, diagnosis and treatment of cancers will also be discussed.

17.2 CLASSIFICATION OF CANCER TYPES

Cancers are often classified according to their tissue of origin. Thus, a carcinoma is derived from epithelial tissue, whereas a sarcoma is derived from tissue of mesodermal origin such as muscle, bone or cartilage. The term leukemia refers to tumors of the bone marrow that result in excess cells of a single type appearing in the blood. Lymphoma refers to a tumor which arises from lymphoid tissue, such as a lymph node. There is also a group of highly malignant tumors that occur in childhood, which all have the suffix 'blastoma'. These include neuroblastomas, which arise in the neuroblasts of the adrenal medulla, retinoblastoma, which originates in the retina of the eye, and nephroblastoma, derived from the embryonic cells of the kidney.

17.3 EPIDEMIOLOGY OF CANCER

In England in 2002 there were 276 700 new cases of malignant cancer registered, approximately evenly divided amongst men and women. However, individual cancers are often unevenly distributed between the sexes and,

clearly, some cancers occur only in men or women. Obvious examples of the latter are cancer of the *cervix uteri* or 'cervical cancer' in women and testicular and prostate cancer in men. Contrary to common belief, men can develop breast cancer, although the incidence is much lower than in women. Moreover, the incidence of breast cancer in both sexes appears to be increasing. A study in the USA showed increases in male and female breast cancer of 26% and 52% respectively between two separate studies in 1973–1978 and 1994–1998. The commonest forms of cancer in men, women and children in the USA are shown in *Table 17.1*.

Men	Women	Children
Prostate cancer	breast cancer	leukemias
Lung cancer	lung cancer	brain tumors
Colorectal cancer	colorectal cancer	lymphomas

Table 17.1 Commonest forms of cancer in the US population

The annual incidence of different forms of cancer is shown in *Figure 17.2*. With the exception of the childhood cancers, the incidence of cancer increases with age, as shown in *Figure 17.3*. This increasing incidence is due to a number of factors including increased length of exposure to environmental agents associated with cancer, and an accumulation within cells of mutations in the DNA (*Chapter 18*), coupled with decreased efficiency of the cellular DNA repair mechanisms. In addition the immune system, which may play a role in eliminating early cancerous cells, also decreases in efficiency with age and this may lead to a failure to eliminate malignant cells as they arise.

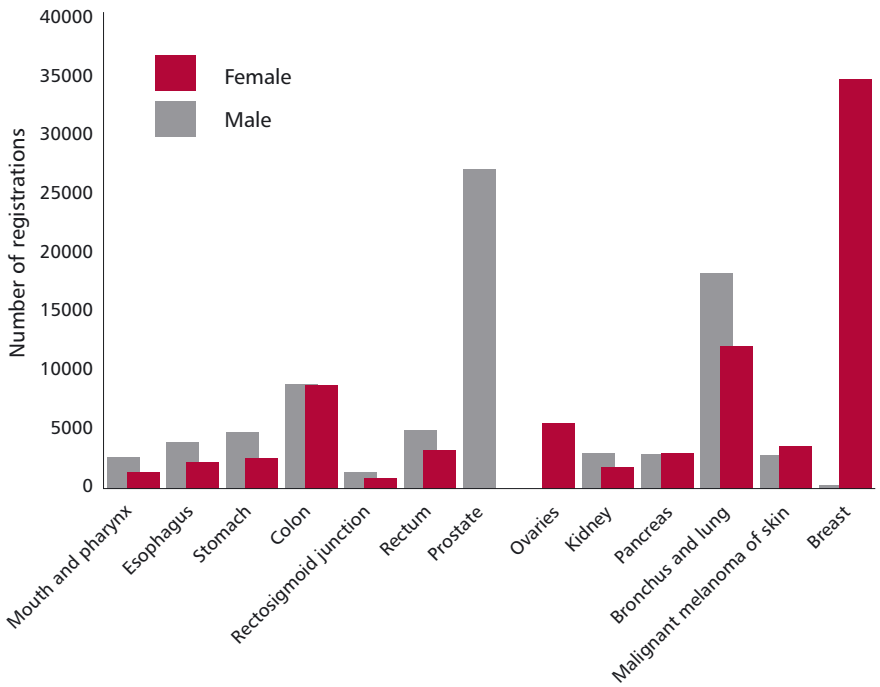


Figure 17.2 **Annual incidence of different forms of cancer in the UK. Statistics obtained from the Office for National Statistics, UK (2005).**

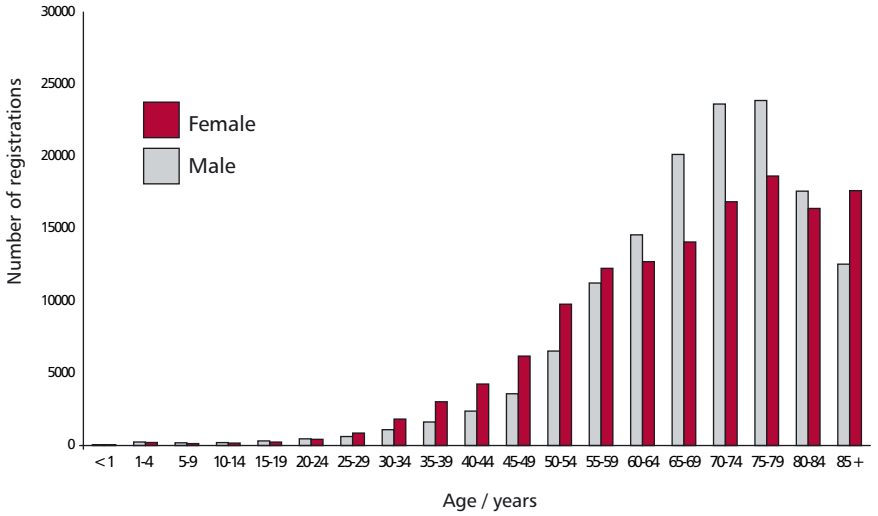


Figure 17.3 The incidence of cancer with age. Based on statistics published in 2005 by the Office for National Statistics, UK.

17.4 MOLECULAR BIOLOGY OF CANCER

In 1914, Boveri (1862–1915) suggested that a malignant tumor arose from a cell that had acquired chromosomal abnormalities. In other words, cancer was caused by mutations in the DNA of cells. The multistep theory of cancer suggests that between five and seven successive mutations may have to occur before a cancer can develop (*Figure 17.4*). Each successive mutation gives the cell a selective growth advantage over the normal cells which surround it. For example, one mutation may confer the ability to grow at a faster rate than normal cells. The cell would then proliferate to form a tissue which is said to be hyperplastic. One of the daughter cells may then undergo another mutation, which allows uncontrolled division of the progeny, to form a mass of cells which have abnormal morphology. At this stage the tumor is known as a carcinoma *in situ*. Accumulation of further mutations within the clone may mean that the cells can detach from the tumor and invade surrounding tissue, that is, they metastasize.

In 2004, a census of published scientific literature showed that 291 genes, representing approximately 1% of the total number of human genes, are associated with cancers. For 90% of these genes, somatic mutations were detected in the cancer cells but not in normal tissue. Approximately 20% of 'cancer genes' show mutations in the germline DNA, which predispose an individual to cancer, while 10% have been associated with mutations in both germline and somatic DNA.

Genes that are associated with cancer include those that control the cell cycle, including cell division and differentiation or molecules involved in signal transduction and associated growth factors, as well as those that control the process of programmed cell death that results in apoptosis (*Chapter 16*). Mutations in some of these genes may lead to increased proliferation and failures in apoptosis. Two major groups of genes linked to cancers are the **oncogenes** and the **tumor suppressor genes**.

ONCOGENES

Oncogenes are mutated forms of normal genes, called proto-oncogenes, which stimulate the increased proliferation of abnormal cells by encoding factors including growth factors and receptors, as well as proteins involved in signal transduction (*Chapter 7*). Examples include *MYC*, *FOS* and the *RAS*

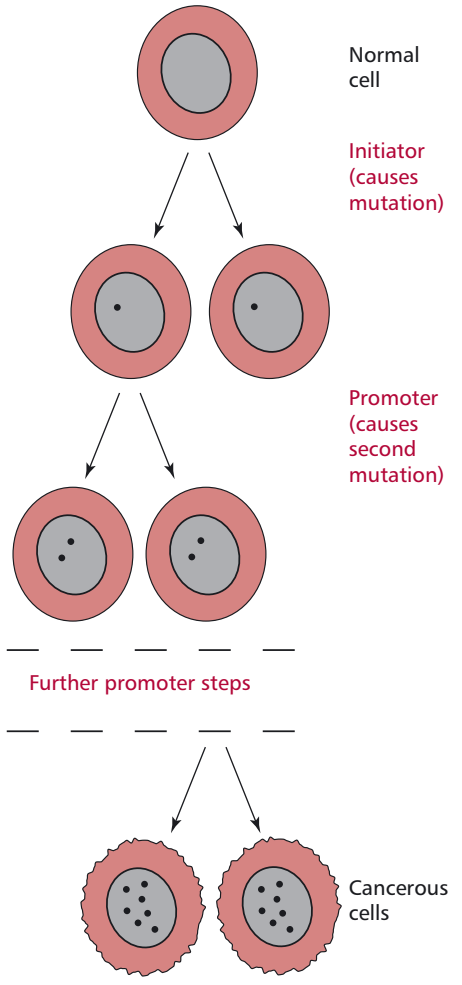


Figure 17.4 Schematic illustrating the multistep theory of cancer.

family of oncogenes. The mutation of a proto-oncogene to form an oncogene usually results in the production of a protein that has increased activity, or in the synthesis of greater than normal amounts of the protein, as, for example, when the gene is continually active. Such mutations are otherwise known as 'gain-of-function' mutations. Oncogenes were first discovered in certain viruses that cause cancer (*Section 17.5*). Some viruses which cause cancer have a gene that is the equivalent of a cellular proto-oncogene. These genes are thought to have been derived initially from host DNA into which the viral DNA was integrated and to have undergone mutation during viral passage. When DNA derived from the virus becomes inserted into the host genome, the viral oncogene may provide the additional signal for cellular proliferation, or may override the normal cellular controls, resulting in the unregulated division of infected cells. The viral and cellular forms of the oncogene are usually distinguished by the prefix '*v*' and '*c*' respectively as in, for example, *v-MYC* and *c-MYC*.

Some examples of oncogenes and associated tumors are shown in *Table 17.2*.

Proto-oncogene	Codes for	Disease
ERB-B1	epidermal growth factor receptor (EGFR)	squamous cell carcinoma of the lung
ERB-B2 (*HER*-2)	growth factor receptor	breast cancer ovarian cancer cancer of the salivary gland
H-*RAS*	GTPase	bladder cancer stomach cancer breast cancer thyroid cancer and others
K-*RAS*	GTPase	stomach cancer pancreatic cancer melanoma bladder cancer neuroblastoma thyroid cancer and others
BCR-ABL	tyrosine kinase	chronic myelogenous leukemia acute lymphoblastic leukemia
SRC	tyrosine kinase	colon cancer
MYC	transcription factor	breast, stomach and lung cancer leukemias
FOS	transcription factor	lung cancer breast cancer

Table 17.2 Some oncogenes and associated tumors

TUMOR SUPPRESSOR GENES

Tumor suppressor genes, in contrast to proto-oncogenes, encode proteins that inhibit the proliferation of cells that contain deleterious mutations. Mutations in the tumor suppressor genes themselves may then lead to a loss of this inhibition that is, they are 'loss of function' mutations. Some examples of tumor suppressor genes are the *TP53* gene, the retinoblastoma susceptibility gene, *RB,* and the Wilms' tumor gene, *WT1*. The *TP53* gene is

Margin Note 17.2 Gene *E2F3*

The gene *E2F3*, which is associated with the development of prostate cancer (*Section 17.8*), was discovered in 2004. The gene encodes a protein that controls cell division. It is produced in appropriate amounts in healthy prostate cells but is overexpressed in prostate cancer cells, leading to their excessive proliferation. The discovery is useful because this protein can be used as a marker for the more aggressive forms of prostate cancer, allowing treatment to be tailored and monitored appropriately.

Margin Note 17.3 *EMSY* and breast cancer

EMSY is a gene involved in regulating the expression of other genes involved in the repair of DNA. It appears to have a role in the development of breast cancer. In 2003, an analysis of more than 500 breast cancers and over 300 ovarian cancers showed that multiple copies of this gene were present in 13% of breast cancers and 17% of ovarian cancers. Women whose tumors carried multiple copies of the gene survived on average for six years after diagnosis whereas those with normal amounts of the gene had a mean survival time of 14 years. Thus, the presence of multiple copies is associated with an aggressive form of breast cancer and a poor prognosis.

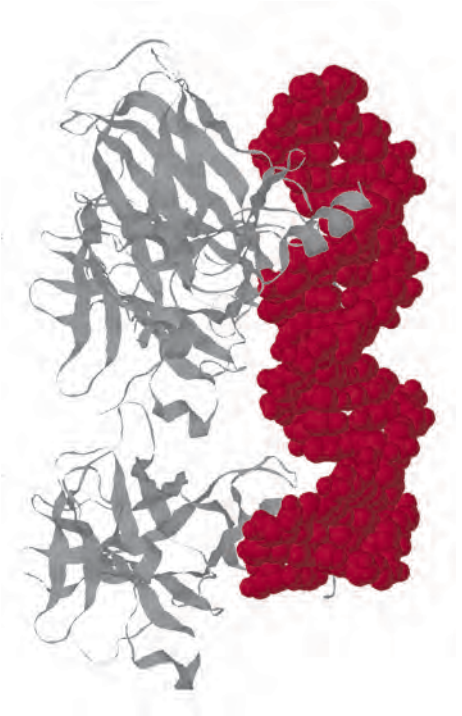


Figure 17.5 A molecular model showing the binding of the p53 protein to DNA (red), this inhibits the division of damaged cells that are potentially cancerous. PDB file 1TUP.

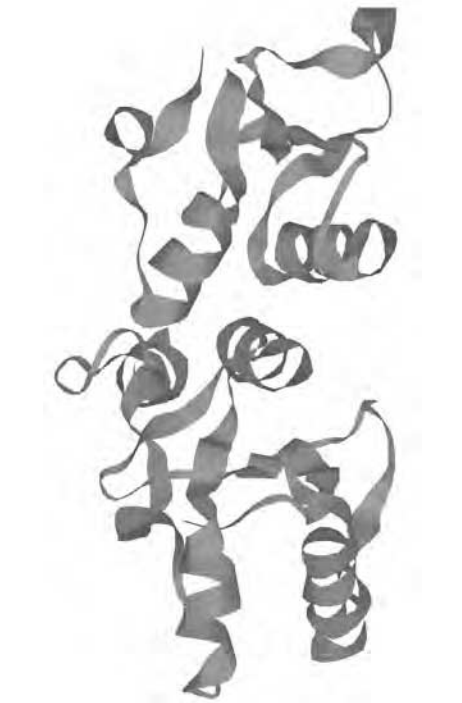


Figure 17.6 Molecular model of a *BRCA1* protein. PDB file 1L0B.

found on the short arm of chromosome 17 and encodes a phosphoprotein, called tumor suppressor protein p53 (*Figure 17.5*) which has been called the 'guardian of the genome'. The gene becomes activated in cells where DNA has become damaged, leading to the production of p53 protein. The protein can bind to DNA, blocking division of damaged cells and inducing apoptosis, thus preventing replication of potential tumors. Mutations in *TP53* can lead to the production of a defective p53 which cannot recognize binding sites on DNA. Thus the replication of the cell is not inhibited, leading to a failure to remove damaged and potentially malignant cells.

17.5 CAUSES OF CANCER

The mutations that lead to cancerous states are caused by or associated with a number of factors. These include mutations caused by errors in replicating DNA or failures in repairing damaged DNA, or they may be induced by a variety of environmental agents, including chemical carcinogens and ionizing radiation or by the action of some viruses. Mutations in cancer associated germ-line genes may also mean that offspring carrying the gene are more susceptible to developing cancer.

INHERITED CANCERS

The association between the inheritance of a mutated gene and the development of cancer genes may be direct or indirect. For a direct association, the offspring must inherit a mutated gene which confers increased susceptibility to a specific type of cancer. With an indirect association, the inherited gene is associated with defective mechanisms for the repair of DNA that, in turn, leads to a greater likelihood of cancer. An example of the latter occurs in people with the disease xeroderma pigmentosum in whom a failure to repair ultraviolet light-induced mutations in the DNA of skin cells leads to the development of multiple skin cancers.

Examples of cancer associated genes with a direct effect include the genes *BRCA1* and *BRCA2*. Mutations in these genes, which are associated with an increased susceptibility to cancer of the breast and ovaries, account for less than 2% of all breast cancers. However, patients with a defective *BRCA* gene have a much greater risk of developing breast cancer than those who do not. *BRCA1* was mapped to chromosome 17q21 in 1990 and at least 100 mutations have been identified in the gene. Women who inherit a mutated *BRCA1* gene have a 60–83% chance of contracting breast cancer at some stage and a 20–40% chance of developing ovarian cancer. This gene has now been sequenced and its product identified. It encodes a transcription factor (*Figure 17.6*) that regulates the expression of, amongst others, the tumor suppressor gene *TP53*. Thus the presence of a mutated gene encoding a defective transcription factor leads to a failure to eliminate damaged cells. Women carrying a mutated form of *BRCA1* may be offered a **prophylactic bilateral mastectomy**, that is the removal of the apparently healthy breasts to prevent the development of breast cancer.

The *BRCA2* gene has been mapped to chromosome 13q12. Mutations in this gene confer a 40–60% chance of developing breast cancer and a 10–20% risk of ovarian cancer at some stage in their lives. A mutated *BRCA2* gene also increases the risk for male breast cancer.

Another gene associated with breast cancer is *CHK2*, which encodes a protein kinase, called the checkpoint kinase. This enzyme is involved in the control of the cell cycle (*Chapter 15*). Inheriting the abnormal variant of *CHK2* doubles the risk of a woman developing breast cancer, in that the variant form is present in 1.9% of women with breast cancer and 0.7% of healthy women.

BOX 17.1 Li-Fraumeni syndrome

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant syndrome that is inherited in typical Mendelian fashion (*Figure 17.7* and *Chapter 15*) which predisposes the patient to cancer. Li-Fraumeni syndrome has been linked to mutations in *TP53*. More than 60% of members of LFS families have inherited mutations in one of the two copies of this gene. Mutations can occur spontaneously in germ cells of one parent or may occur early in the development of the embryo. Some LFS families have a mutation in the *CHK2* gene rather than that encoding *TP53*.

Li-Fraumeni syndrome was first described in 1968, and fewer than 400 families had been identified worldwide by 2006. In LFS families, affected individuals develop cancer at an early age and a wide range of cancers is seen amongst family members. These include cancers of the breast, brain soft tissue, bone and adrenal cortex as well as leukemias, and these are diagnostic. Patients also present with multiple primary tumors at these sites. However, patients within LFS families have also been found to develop tumors at other sites in addition to those used in diagnosis. Children who survive an initial cancer have a high risk of developing a second one.

To diagnose familial LFS, patients must have a number of family members diagnosed with childhood cancer, sarcoma, brain tumor or adrenal cortical carcinoma before the age of 45 years, a close relative (parents, siblings, first cousins) with any LFS associated cancer diagnosed at any age, and another close relative with any cancer diagnosed before the age of 60 years. The age at which patients present with an initial primary tumor is significant since more than half of patients with LFS present before the age of 45, compared with 10% of the general population.

The commonest cancer in females with LFS is breast cancer. Regular **mammography**, which is an X-ray examination of the breast, will detect a tumor as a shadow on the X-ray film or 'breast mammogram' and has been advocated for women in affected families. However, regular X-ray screening is controversial since ionizing radiation itself may increase the risk of cancer in these patients. Prophylactic bilateral mastectomy has also been proposed, though, again, this is controversial since the women remain at risk of developing a cancer at a different location. Genetic counseling of individuals in affected families is essential to inform patients of the potential risks of cancer and to help them develop strategies to avoid at-risk behaviors, such as exposure to radiation.

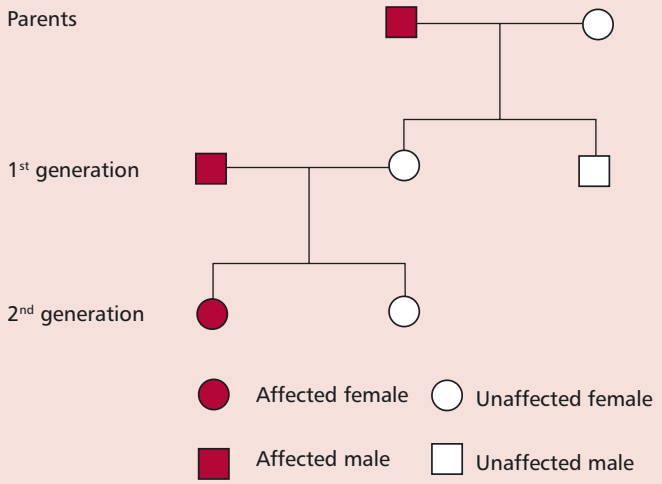


Figure 17.7 Scheme showing the autosomal dominant mode of inheritance of the Li-Fraumeni syndrome.

CHROMOSOMES AND CANCER

Chromosomal abnormalities are found in some cancers. For example, about 95% of patients with chronic myelogenous leukemia (CML) have a translocation (*Chapter 15*) involving chromosomes 9 and 22, that is, t(9:22). The translocation results in the production of a longer chromosome 9 and a shorter chromosome 22, commonly called the Philadelphia or Ph chromosome (*Figure 17.8*). The translocation results in the *BCR* gene on chromosome 22 becoming fused with part of the *ABL* gene on chromosome 9. The fused *BCR-ABL* encodes a tyrosine kinase that is continuously expressed, leading to continuous stimulation of proliferation and the development of CML (*Figure 17.9*). The Philadelphia chromosome is also found in 25–30% of adults with acute lymphoblastic leukemia (ALL; *Section 17.8*). In patients, the translocation originally occured in a single bone marrow cell. However, clonal expansion of the cell results in the blood becoming populated with cells bearing the Philadelphia chromosome. During active disease additional chromosomal abnormalities appear and these are indicative of a poor prognosis.

Other chromosome abnormalities have been associated with a wide range of cancers, including breast cancer, prostate cancer and neuroblastoma,

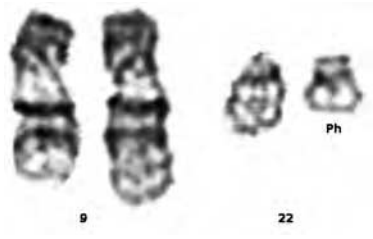


Figure 17.8 The abnormally long chromosome 9 and the Philadelphia chromosome (Ph, abnormal chromosome 22) from a patient with CML. Reprinted with permission of the Wisconsin State Laboratory of Hygiene, University of Wisconsin Board of Regents.

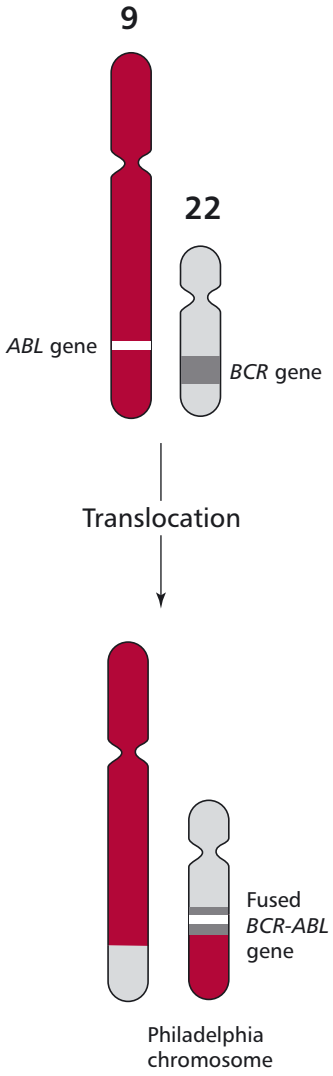


Figure 17.9 Schematic showing the translocation between chromosomes 9 and 22, which results in the Philadelphia chromosome.

but none to the same extent as that found in CML, where the presence of the Ph chromosome is diagnostic for the disease. Some other examples of chromosome abnormalities are shown in *Table 17.3*.

Abnormality	Associated with
Deletion in the short arm of chromosome 1 that is, del(1p)	colorectal adenoma
Deletion on the short arm of chromosome 3 between positions 12 and 14, that is, del(3)(p12;p14)	breast carcinoma
del(3p)	renal cell carcinoma; nonsmall cell carcinoma of lung
Translocation between chromosomes 1 and 17; between position 36 on the short arm of chromosome 1 and position 12 on the long arm of chromosome 17. That is, t(1;17)(p36;q12)	neuroblastoma
chromosome 1 rearrangements	breast carcinomas
del(11)(p13)	Wilm's tumors
t(15;17)	acute promyelocytic leukemia (APL)

Table 17.3 Some chromosomal abnormalities found in different cancers

CHEMICAL CARCINOGENS

In 1775 Potts (1714–1788), an English surgeon, noted the high incidence of scrotal cancer amongst chimney sweeps in London and suggested that this may be related to the accumulation of soot in their clothes. As a result of legislation introduced to ensure that chimney sweeps were able to bathe and to change their clothing regularly, scrotal cancer was eliminated in this profession. In 1918, the Japanese scientists, Yamagiwa and Ichikawa showed that they could induce tumors experimentally by painting coal tar on to the skin of rabbits. This ability of certain compounds to induce tumors experimentally (*Figure 17.10*) led to the identification of many carcinogenic chemicals, including those listed in *Table 17.4*.

The chemical induction of cancers is assumed to be a multistep process, probably involving mutations in several genes, possibly on different chromosomes. Carcinogenic compounds interact with DNA usually by one of a limited number of reactions. For example, alkylating agents such as dialkylnitrosamines and aflatoxin B1 lead to the addition of an alkyl group to electron-rich sites in DNA, as shown for aflatoxin B1 in *Figure 12.4 (B)*. Aromatic amines and amides form highly electrophilic aryl nitrenium ions which also interact with DNA. Polycyclic aromatic hydrocarbons transfer an alkyl group to DNA.

At its simplest, the process of chemical carcinogenesis can be thought to occur in three phases namely: tumor initiation, promotion and progression. During tumor initiation, the carcinogen, or a metabolite of the carcinogen, produces a mutation in the DNA. The cell may repair the damage but misrepair may lead to heritable changes. A cell that has undergone initiation, however, is not yet cancerous because the cell has to 'escape' from normal growth control and become autonomous. Tumor promoters stimulate clonal proliferation of an initiated cell. An example of a promoter is tetradecanoyl phorbol acetate, a constituent of croton oil. Croton oil will promote the development of carcinomas in the skin of mice that have been treated with a single dose of benzo[a]pyrene. Tumor progression involves the additional changes that lead to malignancy and the ability to form metastases.

Chemical	Source	Cancers caused
Aflatoxin	*Aspergillus flavus* and *Aspergillus parasiticum* growing on crops such as corn and peanuts	liver
Arsenic	in insecticides and herbicides	lung, skin
Asbestos	mineral fibers used in fire-insulation, brake linings	mesothelioma
Benzene	petrochemicals, dyes (industrial exposure)	bladder cancer
Benzo[a]pyrene	partial combustion of petroleum; tobacco smoke	lung
Polycyclic aromatic hydrocarbons	partial combustion of petroleum	lung
Polychlorinated biphenols	industrial processes, insecticides	liver, skin
Diethylstilbestrol	once used to prevent miscarriage in women	vaginal tumors in offspring of treated women
Vinyl chloride	industrial processes	liver

Table 17.4 Some carcinogenic chemicals

The targets for chemical carcinogens are the proto-oncogenes and the tumor suppressor genes described in *Section 17.4*. Mutations in *TP53* have been found in more than 500 types of human tumor. The mutations occur at vulnerable sites known as 'hotspots', though the position of the hotspot is not the same for all carcinogens. For example, the metabolite of benzo[a]pyrene preferentially forms adducts with guanine bases (*Figure 12.4 (A)*) at codons 157, 248 and 273 of *TP53*, which are the same mutational hotspots found in human lung cancers. This therefore supports the link between smoking and lung cancer that was established in the 1950s (*Box 17.2*). Some chemical carcinogens may work by promoting the generation of reactive oxygen intermediates which themselves attack DNA. Thus health food shops promote the sale of supplements which are known to remove or 'scavenge' these free radicals. Alternatively some carcinogens may interfere more directly with the regulation of cell proliferation or receptor-mediated cell signaling processes.

Testing for potential carcinogens

The commonest test for the ability of chemicals to cause mutations in DNA is the Ames test which uses a mutant of *Salmonella typhimurium* that is unable to grow on growth media in the absence of the amino acid histidine (*Figure 17.11*). The test involves exposing the bacterium to the chemical in question, usually in the presence of an extract of mammalian liver to provide enzymes that may activate any procarcinogens present. Mutations caused by the potential carcinogen may result in the reversion of the mutant bacterium into one that can synthesize histidine and thus grow on the histidine deficient medium.

Mutagenicity can also be tested by determining the ability of the chemical in question to cause cytogenetic changes in the bone marrow of rodents. Traditional tests for carcinogenicity have ultimately relied on the use of laboratory animals, though this has obvious ethical implications. Some chemicals result in the induction of tumors in the majority of experimental animals after a single dose. The required time for a tumor to develop is known as the latency period and this may be shortened by administering several doses of the carcinogen.

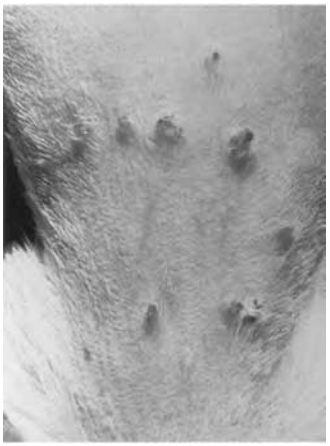


Figure 17.10 Carcinogen-induced tumors on the skin of a rat.

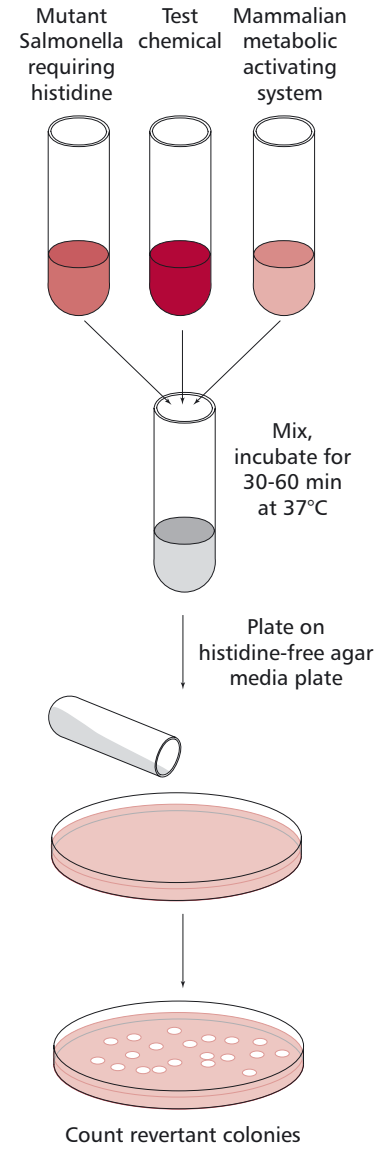


Figure 17.11 Schematic to show the Ames test. See main text for details.

BOX 17.2 Cigarettes and cancer

In the 21st century the link between smoking and cancer is well known. In the USA, smoking accounts for about 30% of all deaths from cancer. As well as being an established cause of lung cancer, smoking is also implicated in the development of cancers of the mouth, esophagus, bladder and pancreas. Other associations link smoking to increased risk of cancer of the stomach, liver and kidney and in the development of CML.

The link between smoking and lung cancer was first established by the renowned scientist and epidemiologist, Doll (1912–2005). Doll qualified in medicine in 1937 and, after World War II, began work on a project to determine the causes of a sharp increase in the number of deaths from lung cancer over the previous 30 years. He embarked on a study in which he gave questionnaires to lung cancer patients about their habits. Originally, he thought the increase might be due to exhaust fumes from cars. From a relatively small scale study to one which involved questionnaires sent to over 60 000 doctors, he and his colleague, Hill (1897–1991), were able to show that the risk of lung cancer was proportional to the number of cigarettes smoked by the patient (*Figure 17.12*) and that long-time smokers had three times the mortality rate of nonsmokers. In addition, he established the link between cigarette smoking and a number of other serious diseases such as coronary thrombosis (*Chapter 14*) and chronic bronchitis.

Cigarette smoking accounts for nearly 90% of deaths from lung cancer and contributes to deaths from other forms of cancer including those of the larynx, mouth and esophagus; smokers are twice as likely to develop bladder cancer as nonsmokers. Fortunately, knowledge of the link between smoking and cancer has led to fewer people smoking in the developed world although the number of younger women who smoke is still increasing, as it is in parts of the developing world.

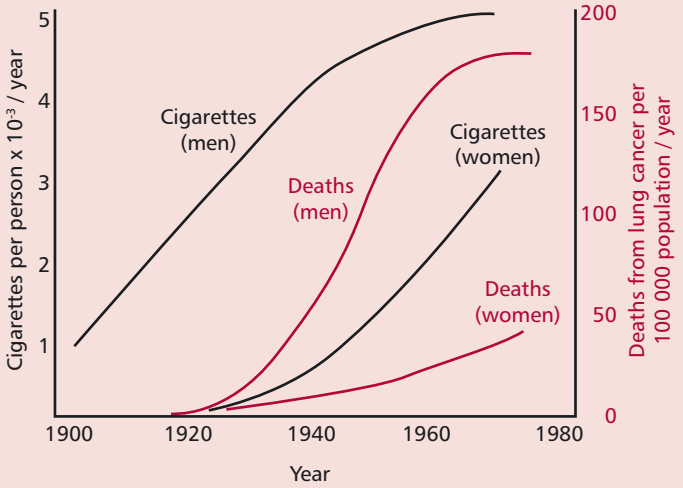


Figure 17.12 The relationship between deaths from lung cancer and the number of cigarettes smoked. Note the 20-year lag between the increases in cigarettes smoked and the increasing numbers of deaths.

Doll used epidemiological studies to establish other links between social habits and clinical conditions. For example, he showed that imbibing alcohol during pregnancy can have undesirable effects on the unborn baby and that exposure to relatively small amounts of ionizing radiation increases the risk of leukemia.

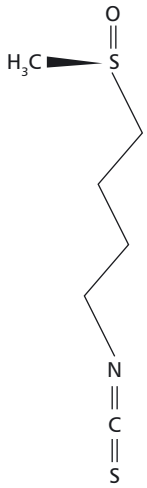


Figure 17.13 The structure of sulfurophane.

DIET AND CANCER

It has been estimated by bodies such as the World Cancer Research Fund that between 30 and 40% of cancers could be prevented by eating a healthy diet, and by maintaining a healthy body weight, (*Chapter 10*) and participating in adequate physical activity. Conversely, prospective studies, in which researchers analyzed the diet and activity of a group of individuals, then monitored the frequency of cancer deaths in that group, have indicated that being overweight or obese contributes to 14% and 20% of deaths in men and women respectively. In addition, obesity has been strongly linked to a variety of cancers, including those of the GIT, liver, prostate, breast, uterus, cervix and ovary. There is also evidence to suggest a link between the consumption of foods with a high glycemic index (*Chapter 10*) and an increased incidence of cancer.

The consumption of low fiber, highly processed foods has a well-established association with the incidence of colorectal cancer (*Section 17.8*) though the link may be more complex than was originally thought. Indeed, an increased consumption of fiber-rich foods, such as fresh fruit and vegetables, has been correlated with a reduced incidence of several types of cancer, including those of the mouth, esophagus, lung and stomach in addition to those of the colon and rectum. Such associations have led to the recommendation by the UK Department of Health that individuals should consume at least five portions of fruit and vegetables a day. Cruciferous vegetables such as cabbage, cauliflower, broccoli and brussel sprouts contain sulfurophane (*Figure 17.13*), a chemical

with anticancer properties. Increased consumption of such vegetables is inversely related to the incidence of breast and bladder cancers.

A number of nutritional interventions appear to offer some protection against cancer. These include decreasing the consumption of red meat and processed red meat, the intake of which is significantly linked to colorectal cancer. Increasing the consumption of ω-3 fats such as α-linolenic acid, (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and decreasing that of ω-6 fats such as linoleic acid (*Chapter 10*) is also recommended. Flax seeds, which are a good source both of dietary fiber and ALA, have been shown to reduce the development of carcinogen-induced tumors and to reduce the rates of metastasis in animal models. Numerous studies have indicated that a sufficient vitamin D (*Chapter 10*) status offers protection against a variety of cancer types, and that improvements in its intake by, for example supplementation, could reduce the incidence of cancer and the associated mortality. Consumption of selenium, which is present in the active sites of several enzymes including the antioxidant enzyme glutathione peroxidase (*Chapter 10*), has been associated with a decreased risk of prostate cancer in men. Other studies have suggested that antioxidants, such as those found in green tea, are protective against cancer, although this is controversial. In addition a high consumption of lycopene (*Figure 17.14*), a carotenoid found in tomatoes, has been shown in several studies to be associated with a decreased incidence of prostate cancer.

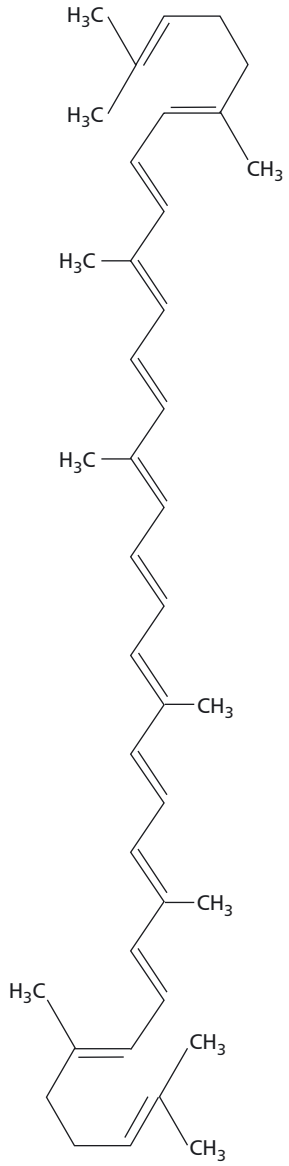


Figure 17.14 The structure of lycopene.

RADIATION AND CANCER

Ionizing radiation can promote the production of tumors *in vivo*, and the transformation of cultured cells *in vitro* from a normal to a malignant phenotype. Some of the evidence for radiation-induced carcinogenesis comes from studies of Japanese people irradiated during the atomic bomb explosions in Hiroshima (*Figure 17.15*) and Nagasaki, and from populations irradiated in nuclear accidents such as that which occurred in Chernobyl in 1986. Long-term studies of Japanese atom bomb survivors showed an increase in the incidence of leukemias in the first 5–10 years following exposure. The risk of solid tumors in these people was also increased significantly. Studies by Doll (*Box 17.2*) showed that infants previously subjected to X-irradiation *in utero* had an increased risk of developing leukemias and solid tumors.

The condition xeroderma pigmentosum also provides evidence for radiation-induced carcinogenesis. These patients suffer multiple skin cancers caused by the failure of their cells to repair ultraviolet light-induced damage to DNA. In addition, normal cells in culture may be transformed by irradiation into cells with a cancerous phenotype. Such studies have been used to analyze the nature of radiation-induced carcinogenesis.

DNA is also the target of ionizing radiation in radiation-induced carcinogenesis and the damage caused includes deletions, inversions and translocations (*Chapter 15*). Irradiation is also known to induce gene amplification and to increase chromosomal instability and these, in turn, increase the likelihood of mutations occurring. Ultimately, mutation events involving proto-oncogenes and/or tumor suppressor genes are the most likely causes of radiation-induced carcinogenesis.

With some exceptions, cells are more susceptible to radiation-induced damage when dividing and this fact has been utilized in the use of radiation to treat cancer (*Section 17.7*).

Figure 17.15 Hiroshima: the Peace Memorial Park.

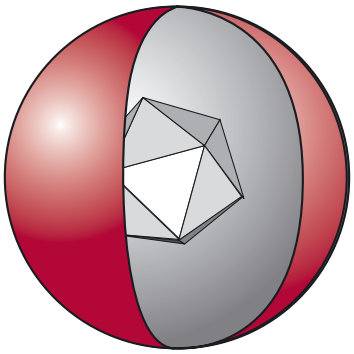


Figure 17.16 Schematic showing an Epstein-Barr virus. The particle is approximately 100 nm in diameter.

VIRUSES AND CANCER

Viruses were first implicated in the development of some types of cancer when it was shown by Rous (1879–1970) in 1911 that leukemia in chickens was caused by a 'filterable agent'. This virus, which causes sarcomas in chickens, is now called the Rous sarcoma virus and has been used extensively in research into oncogenic, or cancer-inducing, viruses.

Today, viruses are associated with between 10 and 20% of all human cancers. In the 1960s, Burkitt's lymphoma, which is a tumor found in the jaws of children in certain regions of Africa, was found to be induced by a virus later identified as the Epstein-Barr virus (EBV; *Figure 17.16*) or human herpesvirus 4 (*Table 3.1*) which also causes glandular fever, or infectious mononucleosis. The EBV infects epithelial cells and B lymphocytes, causing their transformation. This virus is associated with a number of cancers, including nasopharyngeal carcinoma and Hodgkin's lymphoma, in addition to Burkitt's lymphoma.

Cancer associated viruses belong to several groups, including the retroviruses (retroviridae), the papillomaviruses (papillomaviridae), the hepadnaviruses (hepadnaviridae), the flaviviridae and the herpesviridae (*Table 17.5*).

Class of virus	Examples	Associated cancer(s)
Hepadnaviridae	hepatitis B virus	hepatocellular cancer
Flaviviridae	hepatitis C virus	hepatocellular cancer
Herpesviridae	Epstein-Barr virus Kaposi's sarcoma associated herpes virus	Burkitt's lymphoma Kaposi's sarcoma
Papillomaviridae	human papilloma viruses	cervical cancer
Retroviridae	human T-cell leukemia virus (HTLV)	adult T-cell leukemia

Table 17.5 Some viruses associated with human cancer

Retroviruses are RNA containing viruses that have reverse transcriptase activity. When they infect a cell, the reverse transcriptase transcribes their RNA into DNA which may become incorporated into the host genome. Not all retroviruses cause cancer but those which do are called 'transforming retroviruses'. The human immunodeficiency virus (HIV) is a retrovirus that is also associated with cancer, although in this case the association is indirect. People with HIV who develop full-blown acquired immunodeficiency syndrome (AIDS; *Chapter 3*) have an increased incidence of tumors, such as lymphoma and Kaposi's sarcoma, which are associated with EBV and Kaposi's sarcoma virus (KSV). It is likely that the immunosuppression caused by HIV allows latent viruses such as EBV to escape immunological control. Kaposi's sarcoma virus is also associated with nonHodgkin's lymphoma and oral squamous cell carcinoma.

The most widely recognized association between viruses and cancer occurs with certain strains of human papilloma virus (HPV; *Figure 17.17*) that are linked to the development of cervical cancer. More than 70 papilloma viruses have been found in humans. The genomes of these viruses all have a similar structure and contain at least seven 'early' genes (E1–E7) and two 'late' genes, L1 and L2 (*Figure 17.18*). Some HPV subtypes invade epithelial cells of the skin, causing warts while others infect the genital tract and cause benign warts, with low risk of cancer. Others, such as HPV 16, 18, 31, 33 and 45, are associated with the development of cervical cancer in women and are regarded as 'high risk' for inducing cancer. DNA from at least one of these 'high-risk' types is detected in approximately 90% of human cervical cancers. The HPV E6 and E7 genes are

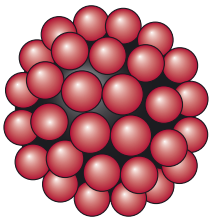


Figure 17.17 Schematic showing a human papilloma virus. The particle is approximately 55 nm in diameter.

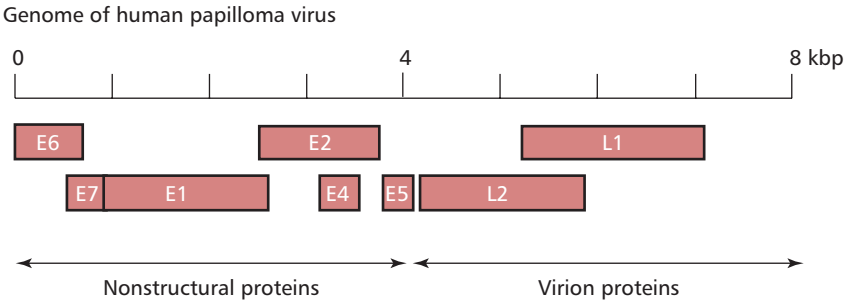


Figure 17.18 **The genes of a human papilloma virus.**

viral oncogenes and the proteins they encode inactivate certain regulators of cell division, such as the tumor suppressor protein p53 (*Section 17.4*). Cervical cancers develop from precursor 'lesions' that are graded high to low according to how much disruption of epithelial cell differentiation has occurred (*Figure 17.19*). In cervical carcinomas, viral DNA becomes integrated into the host genome. However, many benign lesions also contain these strains of HPV, so the presence of the virus alone is insufficient to cause cancer. It seems that long-term infection with HPV predisposes the individual to cervical cancer and that other agents, for example the carcinogens in cigarette smoke, are required to allow the tumor to progress to full malignancy.

17.6 GENERAL DIAGNOSIS OF CANCER

The symptoms of cancer at presentation depend on the location and extent of the tumor. Depending on the cancer, symptoms may develop when the cancer is relatively small as, for example, when even a small tumor of the brain causes pressure to develop. Other tumors, such as those developing in the ovary may not produce symptoms until it is relatively large.

A number of general signs may alert an individual to the presence of an undiagnosed tumor, for example, an unexplained weight loss of about 5 kg or more. Weight loss that occurs as a result of cancers is due to the release of cytokines from cells of the immune system. In end-stage cancer, this weight loss is known as **cachexia** (*Box 17.3*). Fever, which is also induced by cytokines, is often found in patients with advanced cancer, although this may also be an early warning of certain types of cancer. An example of this is Hodgkin's lymphoma, which is characterized by fever, often during sleep, and is accompanied by drenching night sweats. Fatigue may also be a symptom, particularly where the cancer causes a loss of blood with concomitant anemia, as may occur, for example, with stomach cancer. Other signs and symptoms include the presence of a lump, as for example in the breast or testicles, or unusual bleeding or discharges.

CLINICAL TESTS FOR CANCER

Clinical tests for cancer are used to screen for cancer in an 'at-risk' population, to detect cancer in a patient presenting indicative symptoms, to monitor the success of treatment or to detect recurrence in a patient who has been in remission. These tests fall into a number of categories. They may involve the detection and/or quantification of tumor associated molecules, the detection and localization of tumors within the body, and the histological examination of biopsies from suspect tissue to determine the nature of the tumor and/or to detect precancerous conditions.

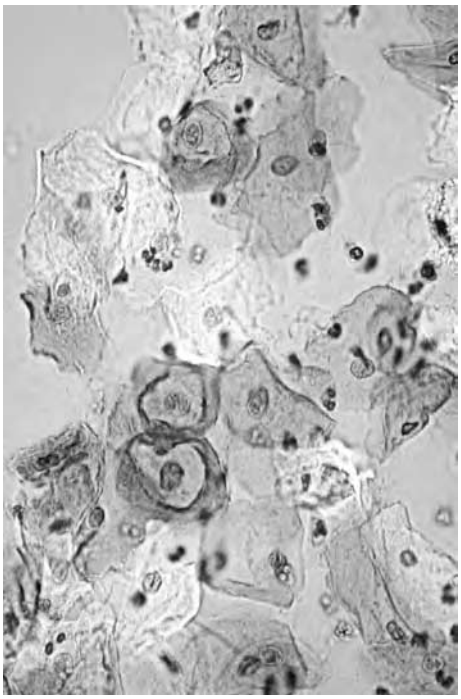


Figure 17.19 **Light micrograph of a cervical smear showing lightly stained squamous cells from the superficial layer of the cervix and more darkly stained cells from the layer of the cervical wall immediately below that of the squamous cells. Note that these cells are abnormal in having comparatively large nuclei and show that the patient is at risk of developing cancer of the cervix.** See also *Figure 1.15*. Courtesy of H. Glencross, Manchester Cytology Centre, Manchester Royal Infirmary, UK.

BOX 17.3 Cachexia

Cachexia (derived from the Greek words *kakos* meaning bad and *hexis*, condition) is characterized by a severe loss of weight, largely of skeletal muscle mass, in someone who is not actively trying to lose weight. It is marked by fatigue, weakness, ill health and decreased appetite. It is usually a sign of various underlying disorders and is associated with chronic disease such as cancer, AIDS (*Chapter 3*), chronic infectious diseases, such as tuberculosis (*Chapter 4*) or severe malnutrition (*Chapter 10*). About half of all cancer patients lose weight although the extent varies with the type of cancer. At diagnosis, 80% of patients with upper GIT cancers and 60% with lung cancer are already suffering cachexia, although patients with hematological malignancies and breast cancer usually avoid such a substantial loss of weight. Most other solid tumors are associated with a higher frequency of cachexia.

Cachexia is commoner in children and elderly patients and becomes more pronounced as the disease progresses. Its prevalence increases from 50% to over 80% before death. In addition to compromizing a patient's quality of life, it is correlated with poor outcomes. Indeed, cachexia is the main cause of death in over 20% of patients, often due to degeneration of the respiratory muscles.

Cachexia also occurs secondarily because of an inability to ingest or use nutrients, for example from obstruction in the GIT or clinical malabsorption. In cancer, it is often associated with a disordered metabolism, and both tumor and host factors appear to play a major role in its development, although surgery or treatment-related disorders, as in the nausea and vomiting associated with chemotherapy or radiation therapy may also be involved. Patients tend to be insulin resistant and have high basal metabolic rates. Furthermore, the patient's response is analogous to that of a chronic infection (*Chapter 4*) and the immune system secretes Interleukins 1 and 6 (IL-1, 6) and tumor necrosis factor α (TNF-α) also called cachectin (*Figure 17.20*), which stimulate fever, protein and lipid breakdown and the production of acute phase proteins by the liver. Protein and lipid catabolism are also stimulated by the release of proteolysis-inducing factor and a lipid-mobilizing factor called zinc α2-glycoprotein (ZAG) from tumor cells which lead to the degeneration of skeletal muscle and adipose tissues respectively, resulting in cancer cachexia, while supplying the tumor with fuels such as glucose (*Figure 17.21*). This can be detected in a patient by evaluating his or her nutritional status, usually with a combination of clinical assessment and anthropometric tests as described in *Chapter 10*. Body weight, with reference to the normal adult weight, is the usual measure of nutritional status.

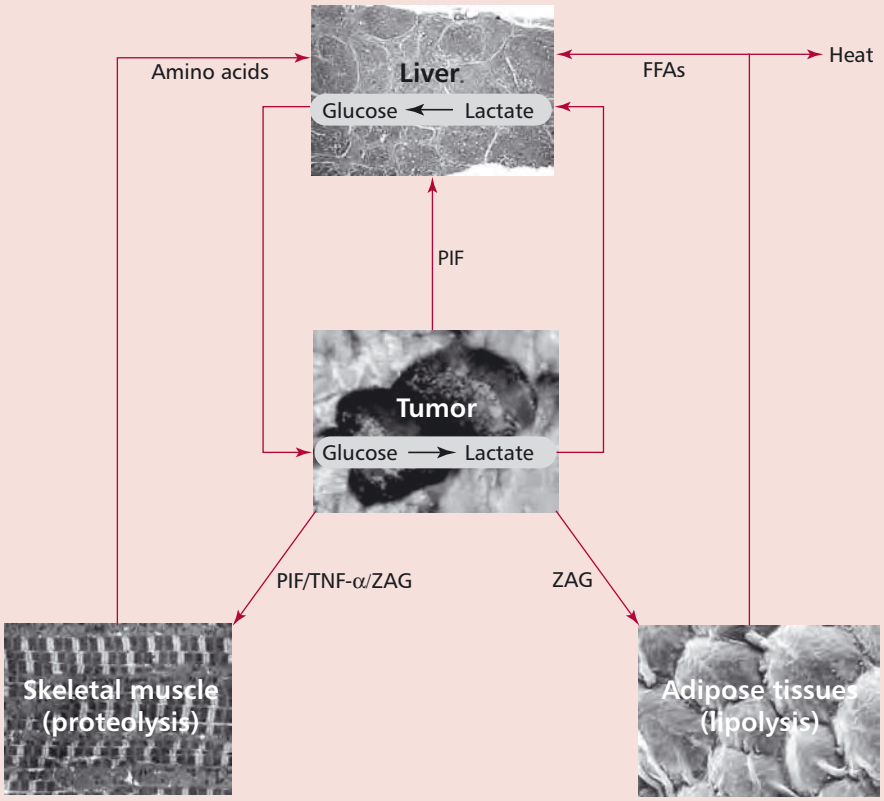
Obviously the best way to treat cancer cachexia would be to cure the cancer. Unfortunately, in adult patients with advanced solid tumors this is often not possible. Treatment should therefore be aimed at improving the quality of life and, for many patients, this means improving appetite and food intake and trying to inhibit muscle and fat wasting. Unfortunately, treatment is limited. Hypercaloric feeding, either enteral or parenteral, does not generally increase lean mass. Glucocorticoids are widely used as palliatives because they inhibit the synthesis and/or release of proinflammatory cytokines such as TNF-α and IL-1, which decrease food intake directly, or through other anorexigenic mediators, such as leptin (*Chapter 10*), corticotrophin releasing factor (CRF) and serotonin and have some limited effect in improving appetite and food intake. Corticosteroids have significant antinausea effects and improve asthenia (weakness) and pain control. However, studies have not shown any beneficial effect on body weight. Indeed, prolonged treatment can lead to weakness, delirium, osteoporosis and immunosuppression, all of which are significant problems initially in advanced cancer patients. The synthetic derivatives of progesterone, megestrol acetate (MA) and medroxyprogesterone acetate (MPA) taken orally have some effect in improving appetite, energy intake and nutritional status. One novel approach under investigation is to use supplements, such as ω-3 fatty acids (*Chapter 10*) that reduce IL-1 and TNF-α production and which may improve the efficacy of nutritional support.

Detection and estimation of tumor-associated molecules

Some types of tumor are associated with increases in tumor associated molecules in the blood. These 'tumor associated antigens' are detected and quantified by using monoclonal antibodies specific for the antigen in question. The antibody may be used in an enzyme-linked immunosorbent assay (ELISA) or in radioimmunoassay (RIA) as described in *Chapter 4*. Examples of tumor associated antigens include prostate-specific antigen (PSA; *Section 17.8*) which is elevated in the blood of patients with cancer of the prostate, and CA 125 antigen, which is found in the blood of women with ovarian cancer. Carcinoembryonic antigen (CEA) is a glycoprotein that is overproduced in most colon carcinomas and in carcinoma of the lung and breast. Serum concentrations are measured and used to monitor treatment and to predict prognosis.

Unfortunately, increases in tumor associated antigens are not exclusive to cancer so that the tests can only give an indication of cancer. Increased

Figure 17.20 Molecular model of cachectin (Tumor Necrosis Factor α). PBD file 1TNF.



FFAs	Free fatty acids
PIF	Proteolysis inducing factor
TNF-α	Tumor necrosis factor α
ZAG	Zinc α2-glycoprotein

Figure 17.21 Some of the physiological activities involved in cancer cachexia.

concentrations should therefore always be followed by further tests, including physical examination and diagnostic imaging.

Detection and localization of tumors within the body

Patients who present with symptoms indicative of cancer may be examined using diagnostic imaging procedures in order to localize the potential tumor or to determine the extent of metastasis. Diagnostic imaging may involve the use of X-rays, computed tomography (CT) also known as computed axial tomography (CAT), magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound, all of which are undertaken by clinical radiologists.

The routine screening for breast cancer by mammography is offered to women in the UK over the age of 50 years. A tumor will show up as a shadow on a breast mammogram. Patients who have lung cancer may have X-rays taken of their bones, in order to determine whether the tumor has spread to them.

Computed axial tomography scanners were introduced into hospitals in the UK in 1975. The technique uses X-rays to take sequential pictures of the body from different directions. In practice, the patient may be required to drink a contrast solution, or this may be administered intravenously, to enhance the tissue contrast. The patient then lies still on a table that passes through the X-ray machine, which rotates around the patient taking pictures of thin 'slices' of tissue. Computers then combine the images to produce three-dimensional images or computed tomograms. Magnetic resonance imaging (MRI) and positron emission tomography (PET), outlined in *Chapter 18*, may also be used to visualize abnormal growths within the body and for determining the extent of tumor growth. Ultrasound (*Chapter 14*) may be used to locate tumors within the abdomen, including tumors of the liver and ovaries. However, in order to determine whether the abnormal growth represents a cancer or a benign lesion, it is essential to examine biopsies of the growth.

Biopsies and histology

Biopsy material may be obtained from a variety of sources in one of several ways. Samples from solid tumors may be obtained by endoscopy, or during surgical procedures involving local or general anesthesia. An endoscope is a long thin flexible tube with a camera and light on the end. Depending on the tumor, the endoscope is inserted into a body cavity and allows internal tissues such as the GIT and the lungs to be viewed. Endoscopes also enable samples of the suspect tissue to be removed without the need for surgery. One example of the use of endoscopy is in bronchoscopy, which is used to obtain biopsies of lung tissue in suspected cases of lung cancer (*Figure 17.22*; *Section 17.8*).

Needle biopsy allows small amounts of tissue to be obtained from a variety of solid tissues. Samples of blood and bone marrow may be examined to detect leukemias. Some solid tumors may cause the build up of fluid containing cancer cells within the peritoneal cavity (*Chapter 10*), where it is known as **ascites** fluid, or in the thorax, where a pleural effusion may develop (*Chapter 14*). These fluids contain tumor cells in suspension and may be examined histologically to confirm the presence of cancer cells. Finally, some precancerous lesions may be detected by taking smears of tissue and examining them histologically, as for example in the preparation of cervical smears in order to detect precancerous lesions as outlined below.

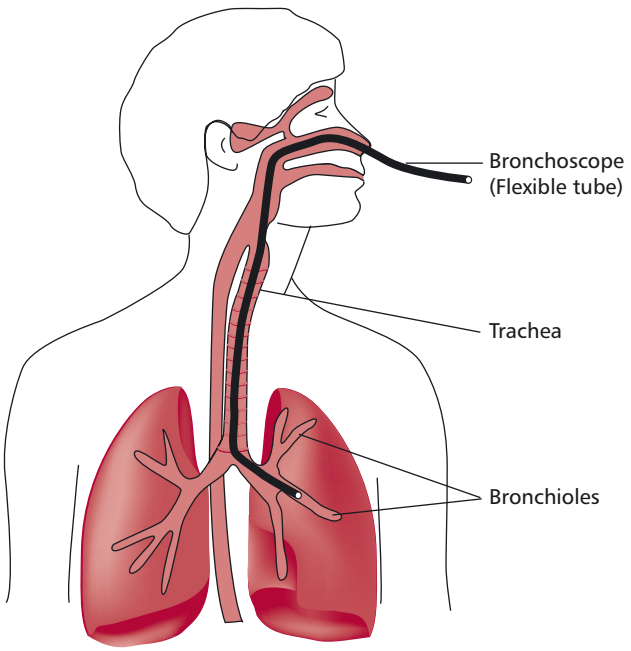


Figure 17.22 Schematic to show a bronchoscopy.

Solid tissue obtained for histological examination must be processed in order to obtain thin sections for microscopic examination. The material is first preserved by fixation in, for example, formalin, and then dehydrated and embedded in paraffin wax to support the tissue. This allows sections between 2 and 7 µm thick to be cut using a microtome. The sections are then mounted on slides, dewaxed with xylene, rehydrated and then stained in the manner appropriate to the investigation. The commonest stains for tissue sections are hematoxylin and eosin. Hematoxylin stains the nucleus purple/black depending on the formulation, while the eosin stains the cytoplasmic contents pink. Hematoxylin and eosin allow good differentiation within the tissue (*Figure 17.23*). Smears of blood and bone marrow are most frequently stained with May-Grunwald-Giemsa, which stains the nuclei blue, while the cytoplasmic contents stain differentially depending on the cell type. This stain therefore allows differentiation between different types of leukocytes. The stain commonly used to detect precancerous cells in cervical smears is the Papanicolaou stain, or Pap stain as it is more frequently known. This formulation contains five different stains: hematoxylin, which stains the nucleus, Orange G (OG-6) and EA, which contains light green, eosin Y and Bismarck brown Y. Orange G and EA are counterstains. The Pap stain is often used to stain buccal and sputum smears as well as those obtained from the cervix.

The preparation of material from solid tissues for histological examination is a long process. Sometimes a more rapid examination may be required as, for example, when the result of a biopsy is needed during an operation in order to determine the extent of surgery required. In such cases, the biopsy is rapidly frozen to –176°C by immersion in liquid nitrogen. This process hardens the material and allows it to be cut into 5–10 µm sections using a freezing microtome or cryostat. Once the sections have been prepared they can be stained with hematoxylin and eosin without the long procedures required with paraffin sections, often within minutes of removal from the body. Examination will then, hopefully, ensure the appropriate surgical procedure.

It is possible to stain cancer cells more specifically if they bear a tumor-specific marker, such as CEA (*see above*). Cryostat sections are often used for this process, because fixation, wax embedding and clearing can destroy some antigenic sites on the tumor. The sections are stained by immunohistochemistry (*Chapter 4*). In this process, the sections are incubated with a monoclonal antibody to a tumor associated antigen. This specific binding is visualized by incubation with an enzyme-labeled anti-immunoglobulin, followed by a further incubation with the appropriate substrate. For enzyme immunohistochemistry, a colorless substrate is chosen that produces a colored insoluble product. It is now possible to use paraffin embedded sections for immunohistochemistry because the antigenic sites that were destroyed during the preparation process, can be 'retrieved' by microwaving the sections in water, subjecting them to heat at pressure using a pressure cooker or by allowing the sections to be partially digested with a proteolytic enzyme. The length of time required to retrieve the antigenic sites has to be determined by trial and error, using positive and negative control slides.

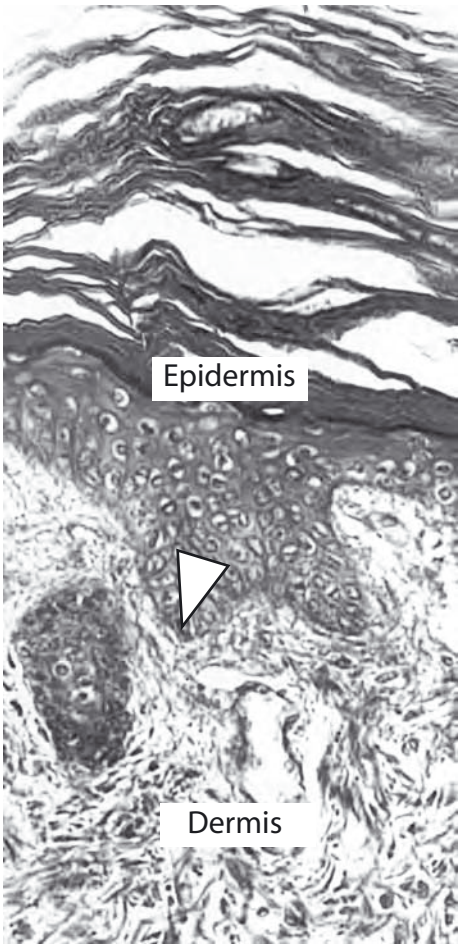


Figure 17.23 Section of skin stained with hematoxylin and eosin. Note the germinative layer of rapidly dividing cells, which is damaged by many anticancer drugs, is indicated by the arrow head.

Molecular diagnosis

The histological diagnosis of potentially cancerous cells is increasingly being supported by molecular diagnostic techniques and it is probable that molecular methods will be used more frequently across a greater range of tumors once the genetic basis for the development of these tumors has been established. The determination of the genetic profile of a patient's primary tumor will no doubt become routine and this will inform treatment and be a predictor of prognosis. One way in which tumors have been investigated

is to extract DNA using a fine needle biopsy, to amplify the DNA by using the polymerase chain reaction (PCR; *Chapter 3*), and to analyze the DNA obtained for mutations known to be implicated in cancer. Fluorescence *in situ* hybridization technique (FISH; *Chapter 4*) is also applied to diagnosis. Thin sections of the tumor are treated to separate the DNA strands which are then hybridized *in situ* with fluorochrome labeled probes for relevant mutated, cancer associated genes (*Figure 17.24*). The slides are then examined using a fluorescence microscope. The presence of the mutation is indicated by fluorescent spots in the nucleus.

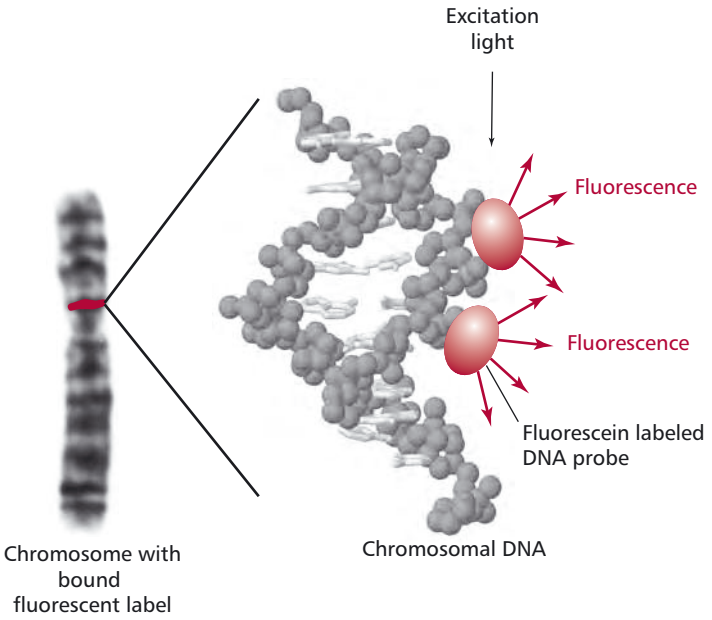


Figure 17.24 Schematic to outline the binding of a fluorescently-labeled DNA probe to target specific chromosomal DNA sequences (FISH). The use of FISH in the specific staining of telomeres is shown in *Figure 18.9*.

17.7 GENERAL TREATMENT OF CANCER

The traditional treatment for primary tumors that have not metastasized to other locations in the body has been surgical excision of the tumor, followed by chemotherapy or radiation therapy (radiotherapy). Chemotherapy involves the use of drugs to kill cancer cells while radiotherapy uses ionizing radiation. However, where a tumor has been diagnosed in an advanced state with metastases in other parts of the body, palliative care only may be given, to ease pain and discomfort.

'Staging' of the cancer is essential as it determines the treatment that the patient receives. Staging of a cancer involves looking at the extent of the cancer within the body. Though staging varies between different types of tumor, a simple system classifies the tumor into one of four stages as shown in *Table 17.6*. Other staging systems include the TNM classification, where T records how far the primary tumor has grown in its original location, N defines whether the tumor has spread to local lymph nodes and M describes whether the tumor has metastasized. The staging of cancers will be discussed further in *Section 17.8*.

The aims of chemotherapy and radiotherapy are to stop the cancer cells from dividing. Other treatments which have been attempted, with varying success include **immunotherapy**, where the objective is to stimulate the body's immune system to eliminate the cancer, as well as a number of 'alternative' therapies all of which are controversial.

Stage	Definition
1	the tumor is small, has not spread to other locations and cannot be felt. The patient is usually free of symptoms and the tumor has been detected by chance during routine medical examination
2	the tumor has not spread from its original location but may be felt during examination or shows up on scans
3	the tumor has spread to adjacent tissues
4	the tumor has metastasized to distant locations

Table 17.6 Staging of tumors

CHEMOTHERAPY

More than 100 different drugs are used to treat different cancers. They are usually given in combination (*Chapter 3*) and with radiation therapy and/or surgery. Most of the chemicals used in the treatment of cancer are, traditionally, those that kill cells, that is they are cytotoxic. Most are active on cells that are dividing, that is they are cycle-dependent. Drugs which kill cells that are not dividing are noncycle-dependent. There is also some evidence that at least some cytotoxic drugs act by inducing terminal differentiation or apoptosis in cancer cells. Many different types of chemicals target cell division in various ways. For example, several categories of drug interfere with DNA synthesis. These include folic acid antagonists, alkylating agents and purine and pyrimidine analogs and the topoisomerase inhibitors (*Chapter 3*). Other drugs inhibit cell division by disrupting the polymerization or depolymerization of microtubules, thus interfering with the separation of chromosomes during mitosis. Unfortunately, drugs that work by preventing cell division do not discriminate between dividing cancer cells and dividing healthy cells. Thus, these drugs have considerable toxicity, particularly towards bone marrow and the epithelial cells of the skin and GIT. Thus, chemotherapy is associated with anemia, nausea and damage to the actively dividing cells of the hair follicles, leading to considerable, but usually reversible, hair loss. A role of the hospital pharmacist is to advise on treatment to minimize the discomfort caused by this therapy. In the treatment of some cancers, aggressive chemotherapy may destroy bone marrow, such that patients require a bone marrow transplant (*Chapter 6*).

The route of administration of chemotherapeutic agents depends on the drug. Many drugs are administered intravenously by infusion. Others are administered intrathecally, that is, by injection into the innermost membrane surrounding the central nervous system. This is usually achieved by lumbar puncture. Administration of chemotherapy in hospitals requires the hospital pharmacist to work alongside the physician so that the most appropriate dose is administered in the most suitable manner. Some of the drugs used to treat cancer are discussed below, although this list is by no means exhaustive. It is worth noting that a natural selection process often takes place within tumors treated with chemotherapy, in that some of the tumor cells may develop resistance to the drug. In cases of drug resistance it is necessary to change the chemotherapeutic agent.

Dihydrofolate reductase (DHFR) is active in the synthesis of tetrahydrofolate, which is required for the synthesis of purines and pyrimidines, themselves required for the synthesis of nucleotides and DNA. Folic acid antagonists inhibit the DHFR and some, such as methotrexate, which is cytotoxic in concentrations between 10^{-7} and 10^{-8} mol dm^{-3} are used in the treatment of cancer. Methotrexate closely resembles the substrate for dihydrofolate reductase and can bind to it, inhibiting its action (*Figure 17.25*).

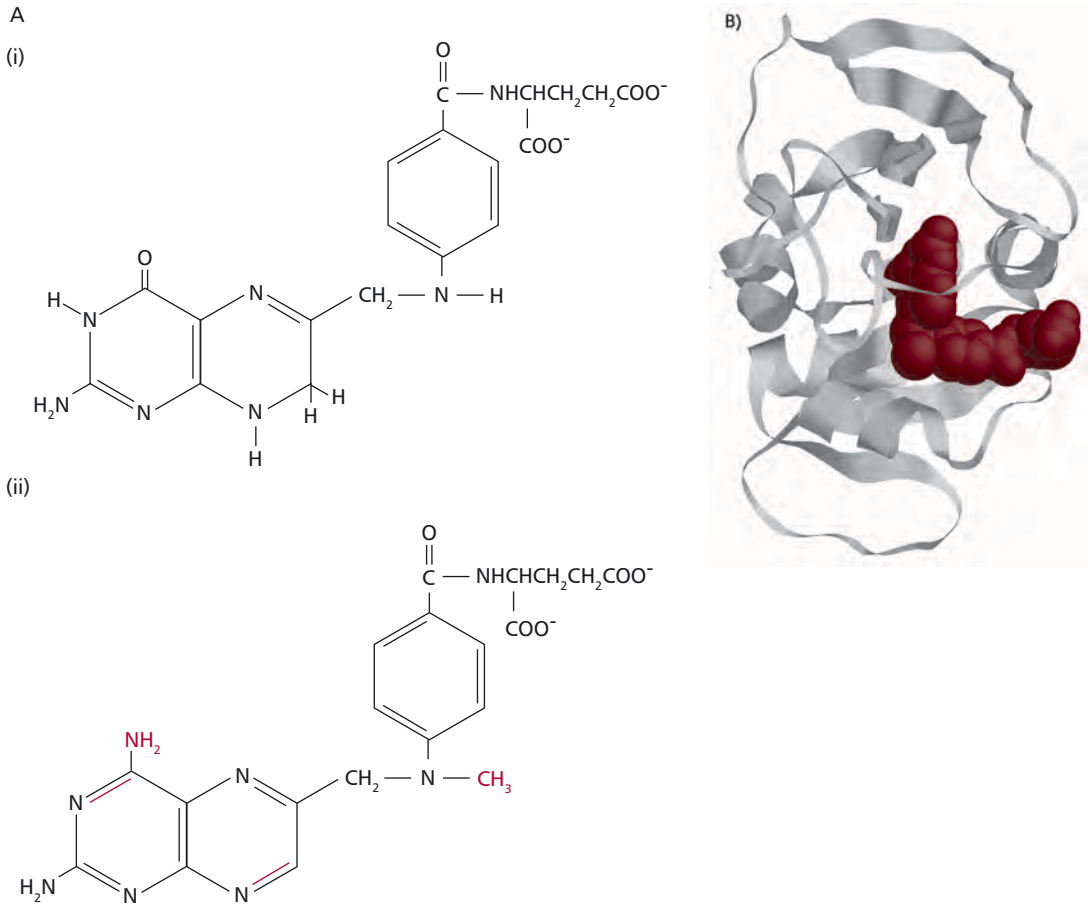


Figure 17.25 (A) Note the similar structures of i) dihydrofolate and ii) the anticancer drug, methotrexate. (B) Molecular model of dihydrofolate reductase with a bound methotrexate molecule. PDP file 1RG7.

Alkylating agents that have two reactive groups are bifunctional and can cross-link two biomolecules. Cross-linking the two strands of DNA is the major cause of toxicity of these drugs since this prevents the separation of the strands which is required for the synthesis of new DNA. Examples of alkylating agents include the nitrogen mustards, such as cyclophosphamide, melphalan, ifosfamide and chlorambucil, and the nitrosoureas, for example *bis*-chloroethyl nitrosourea (BCNU; carmustine) and cyclohexyl-chloroethyl nitrosourea (CCNU; lomustine). Some examples of their use is shown in *Table 17.7*.

Purine and pyrimidine analogs are drugs that resemble one of the bases found in DNA and/or RNA. When present during nucleic acid synthesis, they interfere with the synthesis of DNA, though the site at which they exert their effects depends on the drug itself. Pyrimidine analogs include 5-fluorouracil or 5-FU (*Figure 17.26*) and cytidine arabinoside (ara-C). Purine analogs include 6-mercaptopurine (6-MP) and 6-thioguanine. *Table 17.8* lists some of their uses in cancer treatment.

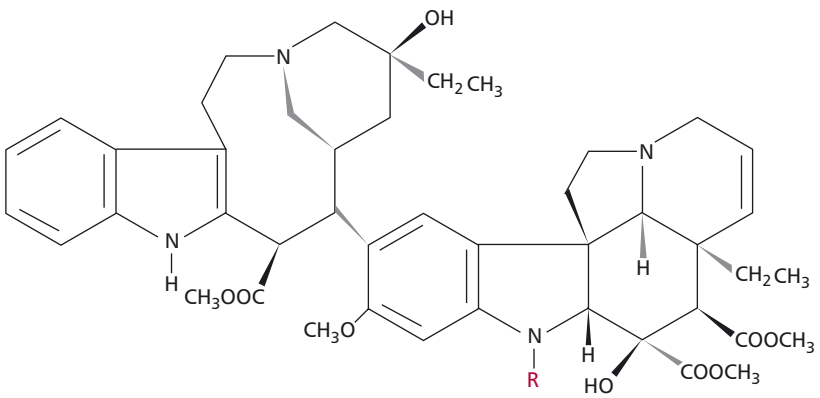
Microtubules form the mitotic spindle, which is essential for the process of chromosome separation during mitosis and meiosis. The formation of a spindle requires microtubules to polymerize from tubulin subunits, whereas separation of chromosomes requires depolymerization. Any drug which interferes with either of these processes will interfere with cell division. The first drug shown to prevent polymerization was colchicine, originally obtained from the autumn crocus, *Colchicum officinale*, though this is too toxic for

Drug	Examples of clinical use
Chlorambucil	chronic lymphocytic leukemia slow growing nonHodgkin's lymphomas;
Melphalan	multiple myeloma
Cyclophosphamide	breast cancer lymphatic cancer
Ifosfamide	testicular cancer lung cancer sarcoma
BCNU	Hodgkin's lymphoma nonHodgkin's lymphoma malignant melanoma multiple myeloma
CCNU	brain tumors Hodgkin's and nonHodgkin's lymphoma

Table 17.7 Alkylating agents in cancer treatment

therapeutic use. The vinca alkaloids vincristine, vinblastine and vinorelbine (*Figure 17.27*), all derived originally from the periwinkle plant *Vinca rosea*, work in a similar manner to colchicine. Vinblastine is used in combination with other drugs to treat testicular cancer, while vincristine is used in treating leukemias. Vinorelbine is used in lung and breast cancer therapy. Paclitaxel, otherwise known as taxol, and docetaxel or Taxotere (*Figure 17.28*) are derived from the bark and needles of the Pacific yew tree, *Taxus brevifolia* (*Figure 15.8 (B)*). These drugs also target microtubules but in this case they prevent their depolymerization. Both drugs are used in the treatment of ovarian, breast and lung cancer.

Topoisomerase inhibitors form a complex with DNA topoisomerase II and inhibit DNA replication. Examples of this class of drugs include VP-16, or etoposide, and VP-26, or teniposide, both of which are derivatives of podophyllotoxin, which is derived from the mandrake plant, *Madragora*. VP-16 is used in the treatment of small cell lung cancer (*Section 17.8*), testicular cancer and lymphomas and VM-26 is used to treat childhood leukemia.



Vinblastine R = CH_3

Vincristine R = CHO

Figure 17.27 Structures of the vinca alkaloids, vinblastine and vincristine.

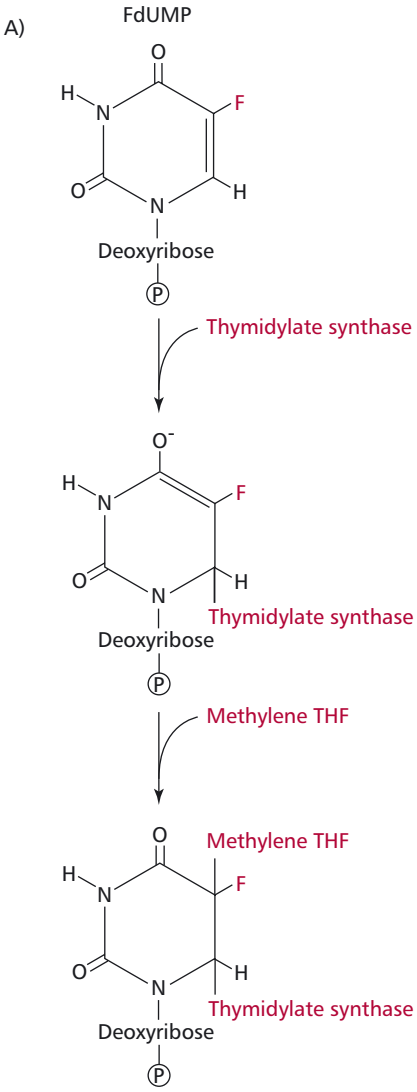


Figure 17.26 (A) 5-Fluorouracil is converted *in vivo* into the anticancer drug to fluorodeoxyuridylate (FdUMP). In the presence of methylene tetrahydrofolate (THF) this binds irreversibly to thymidylate synthase, an essential enzyme for DNA synthesis. (B) A molecular model of thymidylate synthase with a bound FdUMP. PDB file 1TSN.

Drug	Examples of clinical use
5-FU	breast and GIT cancers
Ara-C	acute leukemia
6-MP	acute myeloid leukemia acute lymphoblastic leukemia.
6-TG	acute myeloid leukemia acute lymphoblastic leukemia.

Table 17.8 Purine and pyrimidine analogs in cancer treatment

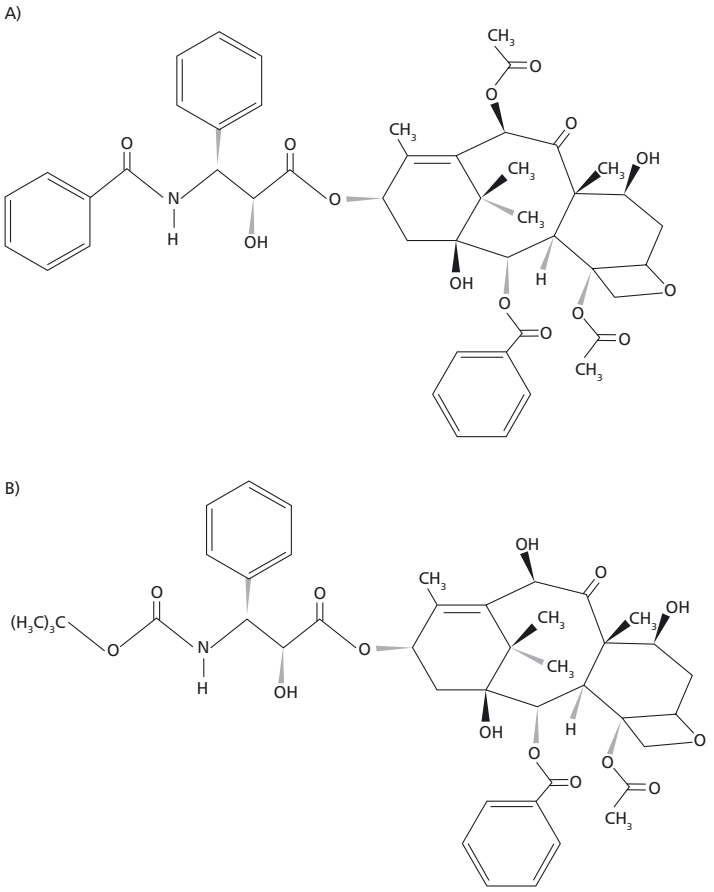


Figure 17.28 Structures of (A) paclitaxel (taxol) and (B) docetaxel (taxotere).

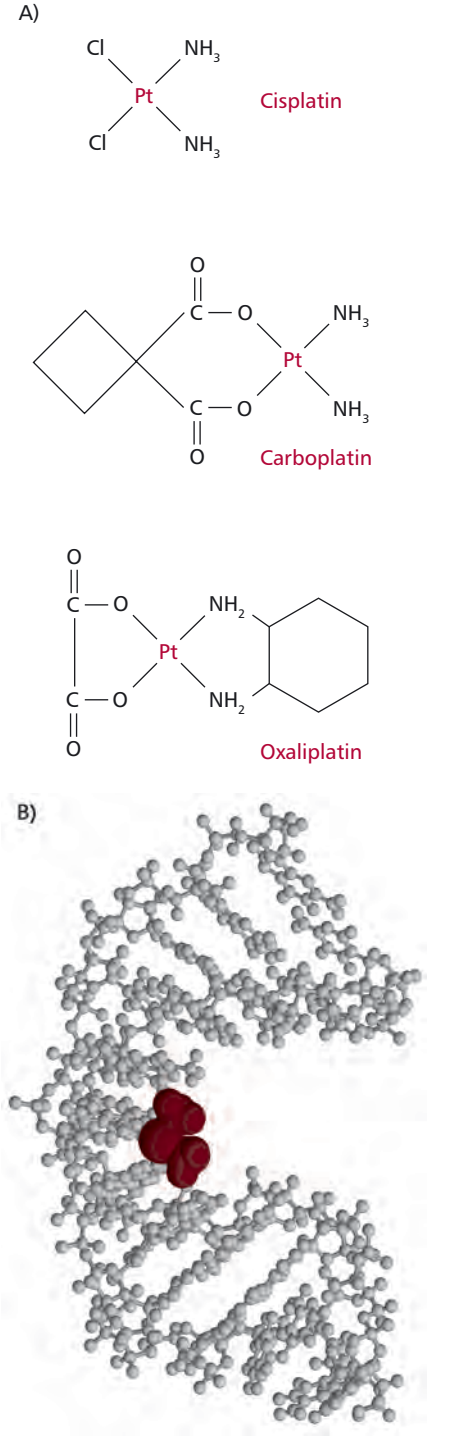


Figure 17.29 (A) Structures of the platinum-based anticancer drugs, cisplatin, carboplatin and oxaliplatin. (B) A molecular model of cisplatin bound to DNA. Note how the double helical structure has been bent and distorted by the binding of the drug. PDB file 1A84.

Cisplatin (*cis*-diamminedichloroplatinum) was first discovered in experiments that showed that the growth of bacteria was inhibited by an electric current delivered by platinum electrodes. This drug is now used in combination therapy to treat testicular cancer. It is also used in treating lung cancer. Other platinum-based drugs include carboplatin and oxaliplatin and all function by binding to DNA, cross-linking the strands and distorting its double helical shape (*Figure 17.29 (A) and (B)*). This facilitates the binding of other proteins to the DNA molecule that mediate toxicity of the drug.

Tumor-specific molecules, on the surfaces of cancer cells may be targeted with monoclonal antibodies (*Chapter 4*). In this way treatment should be more directed at the tumor and general toxicity reduced. Over the years, several approaches have been made to producing targeted therapy using these

antibodies. For example, antibodies have been used to target cytotoxic drugs and toxins such as ricin directly at tumor cells, the so-called 'Magic bullet' therapy. However, since monoclonal antibodies are mouse immunoglobulin they stimulate an immune response in humans. Hence, antibodies have been engineered to contain mouse binding sites but which are carried on human constant regions (*Chapter 4*). Examples of monoclonal antibodies currently in use are trastuzumab (Herceptin), which is licensed for the treatment of secondary breast cancer and which is directed at growth factor receptors on the tumor cells (*Section 17.8*), and rituximab (Rituxan) which is used in the treatment of nonHodgkin's lymphoma.

RADIATION THERAPY

Radiation therapy, which involves the use of high energy electromagnetic waves, is used to treat between 50–60% of cancers. The treatment is based on the fact that most cells are susceptible to radiation when they are dividing. The common side effects of radiation therapy are fatigue, nausea and some external burns to the skin, therefore the dose of radiation needs to be carefully calculated in order to give the optimum antitumor dose with minimal side effects.

Radiation treatment is delivered in one of two ways. With external beam therapy, the area is irradiated with X-rays from an external source. The dose of X-rays is given in short, fractionated daily doses over a period of time, a regimen known as continuous hyperfractionated radiotherapy 'CHART', to allow normal cells to recover. Treatment regimens depend on the size and location of the tumor and the purpose of the treatment, that is, whether it is intended to cure, to shrink the tumor prior to surgery or chemotherapy or to palliate an incurable tumor. With internal therapy the radioisotope is placed near or inside the tumor for a short period of time, a process known as brachytherapy. For example, intracavitary radiotherapy involves the insertion of ^{137}Cesium into a body cavity in an applicator. This form of treatment is used for cancer of the vagina, cervix or uterus. Alternatively, thin radioactive wires may be inserted directly into the tumor, as, for example, in the treatment of prostate cancer. Internal therapy may also involve giving the patient a radioactive liquid either orally or intravenously. For example, a drink of radioactive iodine may be given to treat thyroid cancer. Since the thyroid preferentially takes up iodine (*Chapter 7*), the radioactivity becomes concentrated at the site where it is required. Intravenous radioactive liquids are used to treat metastatic bone cancer.

IMMUNOTHERAPY

The term *immunotherapy* in relation to cancer refers to processes that manipulate the immune system to improve the body's response against a tumor. Immunotherapy has a long history and began in the era before the advent of cytotoxic drugs when cancer patients were treated with Coley's toxin. This contained a mixture of killed *Streptococcus pyogenes* and *Serratia marcescens* bacteria that stimulated the immune system nonspecifically (*Chapter 4*). The BCG vaccine, which contains killed mycobacteria, was used in the 1960s and 1970s, to treat malignant melanoma and has since been used to treat bladder cancer. Mycobacteria are potent stimulators of the immune response and increase the production of several cytokines, including interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α). Nowadays, recombinant cytokines may be given directly to enhance the immune response. For example, interferon α (IFN-α) has been used successfully to treat multiple myeloma, CML, hairy cell leukemia (*Section 17.8*) and malignant melanoma. Interleukin 2 (IL-2) appears to exert an anticancer effect through the prolonged stimulation of Natural Killer cells; it has been used to treat renal cancer and malignant melanoma (*Chapter 4*).

An exciting development in immunotherapy has been the production and clinical trials of a number of anticancer vaccines based on tumor associated antigens. Examples include vaccines based on peptides derived from carcinoembryonic antigens, and the BiovaxID™ vaccine for the treatment of follicular lymphoma, a type of nonHodgkin's lymphoma involving B lymphocytes.

17.8 SPECIFIC TYPES OF CANCERS

Cancer patients, naturally, may present with a variety of symptoms depending on the origin and extent of the tumor. The treatment administered for any cancer patient therefore depends to a large extent upon the type of cancer present, its location, the stage of the disease and the age and health of the patient. Major concerns in the developed world include lung, breast, prostate and colorectal cancers and these are discussed below. The leukemias will also be discussed as examples of tumors arising from bone marrow stem cells.

LUNG CANCER

Almost 29 000 deaths were attributed to lung cancer (*Figure 17.30*) in England and Wales in 2002 and around 37 000 new cases are diagnosed annually. In the USA lung cancer is, again, the second most common malignancy after prostate cancer in men and breast cancer in women, with over 160 000 new cases occurring each year. Worldwide, about one million new cases occur annually, with an incidence of 37.5 new cases per million population amongst men, and 10.8 cases per million amongst women.

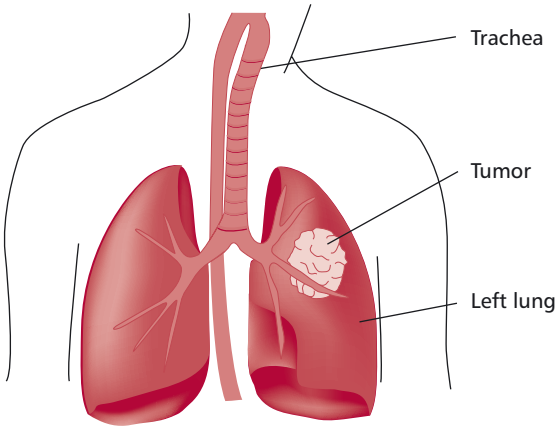


Figure 17.30 Schematic illustrating the presence of a cancer of the lung.

Lung cancer is a fatal disease and, in England and Wales, only approximately 20% and 6.0% of patients survive one year and five years respectively after diagnosis. These figures are higher in the USA, where the five-year survival figure stands at about 14%. Overall, lung cancer is the most frequent cause of death from cancer in men, who make up around 60% of all lung cancer cases. In women, lung cancer is the second commonest cause of cancer death after breast cancer. The risk of lung cancer increases with age with approximately 75% of deaths occurring after the age of 65.

A link between smoking and cancer is indisputable and smoking and passive smoking are the cause of 90% of lung cancers. The carcinogens in cigarette smoke include benzo[a]pyrene, a polycyclic hydrocarbon and *N*-nitrosamines, both of which are metabolized by the cytochrome P-450 enzymes in the liver to carcinogens that form adducts with DNA as described in *Chapter 12*. Radon, a naturally occurring radioactive gas produced from the decay of uranium and which is found at relatively high indoor levels in homes built

of, and on, granite, is also responsible for a small but statistically significant number of cases each year. People who work in uranium mines are also at risk of radon-induced lung cancer. Exposure to the mineral asbestos is also strongly associated with the development of lung cancer and increases the risk of developing lung cancer fivefold.

Classification of lung cancer

Lung cancer is classified into two main groups namely small cell lung carcinoma (SCLC) and nonsmall cell lung carcinoma (NSCLC). Small cell lung carcinoma accounts for about 20% of all lung cancers. The cancer cells are small with a high nucleus to cytoplasm ratio. Nonsmall cell lung carcinomas are comprised of three types, namely squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Squamous cell carcinomas develops from the epithelial cells lining the respiratory tract; they form 35% of all lung cancers. Adenocarcinomas develop from the mucus-secreting cells in the lining of the respiratory tract and account for 27% of lung cancers. Finally, large cell carcinoma, so called because the cells are relatively large and rounded compared with the other forms, accounts for 10% of total lung cancers.

Signs, symptoms, diagnosis and staging of lung cancer

Lung cancer does not generally cause symptoms in the early stages and by the time these occur the disease is generally in an advanced state. Some patients are asymptomatic and may only be diagnosed following a routine chest X-ray. Symptoms at presentation include a persistent and nagging cough, shortness of breath, recurrent chest infections such as pneumonia and bronchitis, coughing up blood-containing sputum or **hemoptysis**, chest pain when breathing or coughing, and an unexplained loss of weight. A patient showing these symptoms should be referred urgently for a chest X-ray and/or a CT scan. If these indicate cancer, the tumor should be staged by scanning patients using positron emission tomography (PET). Other tests include examination of the chest by inserting an endoscope through a small cut at the base of the neck. In addition, biopsy may be taken using a fine needle inserted into the lungs, guided by a CT scanner or X-ray machine.

Staging of the disease is required to determine treatment. The TNM staging system, mentioned in *Section 17.7*, for NSCLC classifies the primary tumor from T1 to T4, where T1 represents a tumor less than 3 cm diameter with no invasion of the main bronchus. Tumors greater than 3 cm that may also involve the main bronchus are classified as T2, while T3 represents a tumor of any size which has invaded the chest wall, diaphragm, mediastinal pleura, parietal pericardium or main bronchus. A T4 stage tumor is one of any size that has invaded any of a range of tissues, such as the heart, trachea or esophagus. The regional lymph nodes are staged as N0 to N3, where N0 represents no regional lymph node metastasis, N1 and N2 represents increasing metastasis to lymph nodes on the same side or opposite side to the tumor respectively. Where distant metastasis has occurred, this is classified as M1. The TNM is further classified into subsets as shown in *Figure 17.31*.

The staging for SCLC is somewhat different with patients being classified as having limited stage disease or extensive stage disease. Limited stage disease is used if the tumor is restricted to one hemithorax and may include patients with lymph node metastasis. Extensive disease is defined as disease at sites beyond the definition of limited disease.

Treatment of lung cancer

For NSCLC, surgery is used to remove the tumor, as directed by the staging. How much of the lung is removed depends on the stage of disease and the health

	T1	T2	T3	T4
N0	1A	1B	IIB	
N1	IIA	IIB	IIIA	
N2	IIIA	IIIA		
N3				

Patient offered surgery if no medical contraindications

Surgery may be suitable for some patients, based on clinical judgment

Not suitable for surgery

Figure 17.31 The TNM classification of nonsmall cell lung cancer. Summarized from NICE guidelines www.nice.org.uk

of the patient. During surgery, lymph nodes are sampled to aid more accurate staging of disease. Radiotherapy is recommended for patients with stage I, II or III disease. Patients with Stage III or IV may be offered chemotherapy although NSCLC is only moderately sensitive to chemotherapy. Chemotherapy for advanced NSCLC uses a combination of drugs such as paclitaxel or docetaxel, together with a platinum drug such as cisplatin. Patients with SCLC are treated with a platinum drug and multidrug regimens. The drug regimen may be given in cycles to patients who respond to treatment. Patients with limited stage SCLC are given radiotherapy concurrently with chemotherapy. Those who have inoperable lung cancer should be given palliative treatments to ease their symptoms. This may include radiotherapy to relieve breathlessness and chest pain, opioids to ease the cough, and procedures to alleviate large airway obstruction.

BREAST CANCER

Breast cancer (*Figure 17.32*) is the commonest cancer in women in both the UK and the USA, and the second leading cause of cancer deaths in women. The incidence of new cases in the UK is about 41 000 per year and in the USA it is just over 210 000, while the annual incidence worldwide is approximately 1.2 million. It is estimated that about one in nine women will develop breast cancer during their lifetime. Breast cancer also occurs in men, though with a much lower incidence. In the UK, around 250 men are diagnosed with the disease each year and approximately 70 die annually of the disease.

Risk factors for the development of breast cancer include increased age, childlessness, early menarche or late menopause, hormone replacement therapy, being overweight or obese, use of the contraceptive pill and regular consumption of alcohol over a long period of time. Breastfeeding reduces the risk of contracting the disease. Familial breast cancer accounts for 5% of all breast cancers and is related to the inheritance of mutated forms of genes such as the *BRCA1* and *BRCA2* genes as described in *Section 17.4*.

Signs, symptoms, diagnosis and staging of breast cancer

Breast cancer develops either in the milk-producing glands or in the ducts that deliver milk to the nipple. Symptoms of breast cancer include a new painless lump occurring in a breast, changes in the size or shape of the breast or in the position of the nipple, a discharge from the nipple, an eczematous rash

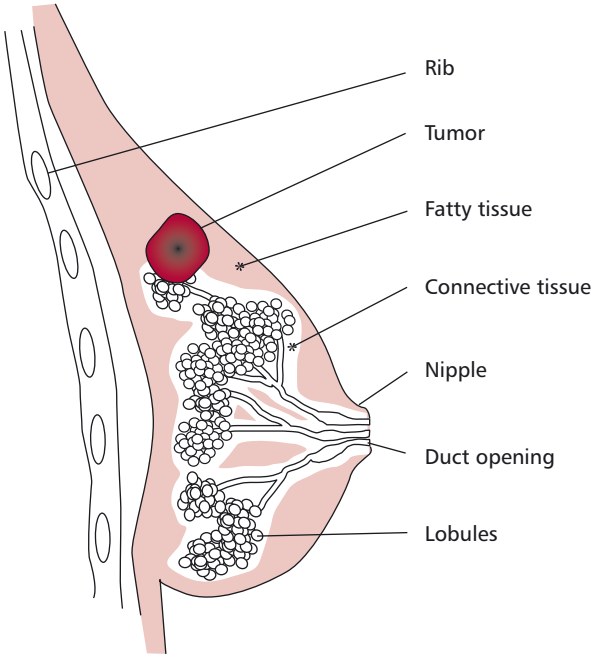


Figure 17.32 Schematic illustrating the presence of a cancer of the breast.

around the nipple or a thickening behind the nipple, puckering or dimpling of the skin of the breast or a swelling or lump in the armpit.

Mammography uses X-rays to locate the position of the potential tumor. Mammography is also used to screen for cancer and, in the UK, this is offered every three years to all women over the age of 50 years. The lump may also be examined by ultrasound or by Color Doppler ultrasound, which gives a picture of the blood supply to the lump. Microscopic examination of cells from a fine needle aspirate of the lump may also be helpful. Alternatively, the lump may be excised under a general anesthetic for pathological examination.

The staging system for breast cancer describes two stages of noninvasive and four stages of invasive breast cancer. Noninvasive stages include ductal carcinoma *in situ* (DCIS) in which cancer cells are contained within the ducts. If diagnosed at this stage, the disease is almost completely curable. Lobular carcinoma *in situ* occurs when cancer cells are restricted to the lining of the breast lobules. Stage 1 invasive cancer describes a tumor measuring less than 2 cm diameter, with no spread to the lymph nodes. In Stage 2 invasive cancer the tumor measures between 2 and 5 cm and/or there are affected lymph nodes. In Stage 3 invasive cancer the tumor is larger than 5 cm diameter and may be attached to muscle or skin. The lymph nodes at this stage are usually affected. Stage 4 invasive cancer describes a tumor of any size, the lymph nodes are usually affected and the cancer has metastasized.

A microscopic examination of cancer cells allows their appearance to be graded. Low grade or Grade 1 cancer cells have the appearance of differentiated normal cells, whereas high grade (Grade 3) tumor cells have an abnormal appearance and are characteristic of fast growing and aggressive cancers. The tumor cells may also be examined immunohistochemically or by FISH (*Section 17.6*) to detect expression of estrogen receptors or HER2 proteins on their surface. Knowledge of the presence of either of these molecules allows the treatment regimen to be determined more appropriately. Cells with estrogen receptors may be stimulated to divide by naturally occurring estrogen, and hormone therapy is indicated. The HER2 protein is a receptor for the human epidermal

growth factor (hEGF). Breast cancers that are positive for HER2 proteins are stimulated to divide by naturally occurring hEGF and some treatments prevent this stimulation and reduce the growth of the cells. In the UK all women with early stage breast cancer are tested for HER2 status of the tumor.

Treatment of breast cancer

The first line of treatment for breast cancer is to remove the tumor. This may involve excision of the lump and some of the surrounding tissue or it may mean mastectomy. Chemotherapy or hormonal therapy may be given to reduce the size of the tumor prior to excision. During surgery, lymph nodes are also removed from the armpit and used for accurate staging of the tumor. Two to four weeks after excision or mastectomy, radiation therapy is used to destroy any remaining cancer cells. Chemotherapy, using a combination of drugs, may be used before and after surgery. If the tumor cells express estrogen receptors hormone therapy, using drugs such as tamoxifen, is given to block the estrogen receptors or to lower the amount of estrogen in the blood. Tumors that are HER2 positive may be treated with trastuzumab otherwise known as Herceptin which was described in *Section 17.7*.

PROSTATE CANCER

The prostate is a small gland, surrounding part of the urethra, which produces semen that mixes with the sperm produced by the testes as described in *Chapter 7* (*Figure 17.33 (A)*). Prostate cancer is a disease that principally affects men over the age of 50 years. Many prostate cancers go undiagnosed because the tumor remains latent for long periods of time. The annual incidence of prostate cancer in the UK is about 30 000 men and around one in 12 men will develop the condition. In the USA the incidence is half that of the UK. Its incidence has increased in recent years, although this may reflect the increasing age of the population. While most prostate cancers are slow growing, a small proportion of tumors grow and metastasize more quickly. The risk of a man contracting prostate cancer are increased if close relatives have had the disease, or if female family members have had breast cancer, especially if they were diagnosed at an early age. Men of Afro-Caribbean and African–American origin are at greater risk of getting the disease while Asian men have the lowest risk. A diet high in animal fat and dairy products and low in fresh fruit and vegetables increases the risk. Consumption of the carotenoid, lycopene (*Figure 17.14*), which is abundant in tomatoes and tomato products, reduces the risk of contracting prostate cancer. Lycopene has been shown to lower the amount insulin-like growth factor 1 (IGF-1; *Chapter 7*), which may otherwise stimulate the growth of cancer cells.

Signs, symptoms, diagnosis and staging of prostate cancer

The symptoms of prostate cancer are not usually present when the tumor is small. However, as the tumor grows there is difficulty and pain on passing urine, coupled with a more frequent need to urinate, particularly at night. There may also be blood in the urine. If cancer cells have spread to the bone there may be pain in the back and pelvis.

A patient presenting with symptoms of prostate cancer will be given a digital rectal examination (DRE; *Figure 17.33 (B)*). During this examination a gloved finger is inserted into the rectum, from where the prostate can be felt. An enlarged prostate that feels round and smooth is most likely a benign prostate hyperplasia. In contrast, a prostate tumor will make the gland feel hard and lumpy. Blood samples are also taken for a PSA test (*Section 17.6*). The PSA test measures the level of prostate specific antigen. The normal level of PSA is approximately 2.8 ng cm^{-3} in men of 50 and 5.3 ng cm^{-3} in men of 70 years of age. Men with levels of 10 ng cm^{-3} or above require referral for further

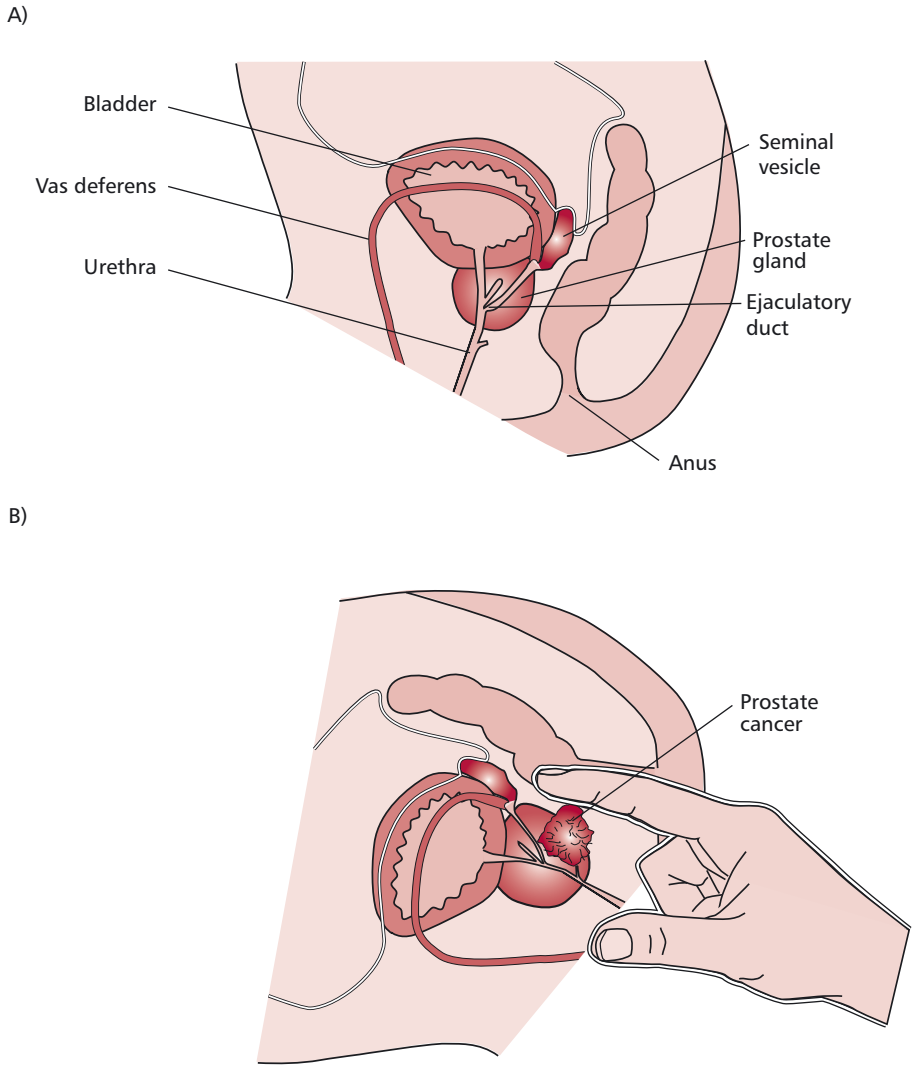


Figure 17.33 Diagrams illustrating (A) the normal appearance of the prostate gland and (B) a rectal examination of a cancerous prostate gland.

tests because above normal levels of PSA are found in conditions other than cancer, for example in urinary infections. Following referral, additional tests undertaken to determine the extent of the problem include an isotopic scan of bones and an MRI or CT scan. Biopsies of the prostate are obtained by passing a needle through the rectum into the prostate, aided by an ultrasound scan.

Prostate cancers are commonly graded using the Gleason system which scores the cancer according to the growth pattern and the arrangement of the cancer cells within the prostate. The higher the score, the more likely the tumor is to spread. The tumors are staged as shown in *Table 17.9* and *Figure 17.34*.

Treatment for prostate cancer

The treatment for prostate cancer is determined by the grade and stage of the tumor, including metastasis, the age and health of the patient and the concentration of PSA in the blood. The range of treatments for early prostate cancer includes surgical removal of the prostate gland or prostatectomy, radiation therapy, hormonal therapy, or combinations of any or all of these. Chemotherapy is rarely used to treat prostate cancer. Depending on the age of the patient, an early stage cancer may not require treatment, but may be actively monitored until treatment is needed. Prostate cancers often grow slowly and the treatments, which have considerable side effects, should

Stage	Description
T1	tumor within the prostate gland too small to be detected during a rectal examination often no symptoms PSA test or biopsy is positive localized prostate cancer
T2	tumor within prostate gland large enough to be detected at rectal examination often no symptoms localized prostate cancer
T3/4	tumor has spread into the surrounding tissues locally advanced prostate cancer
Metastatic cancer	lymph nodes, bones or other parts of the body affected advanced prostate cancer

Table 17.9 Staging of cancers of the prostate

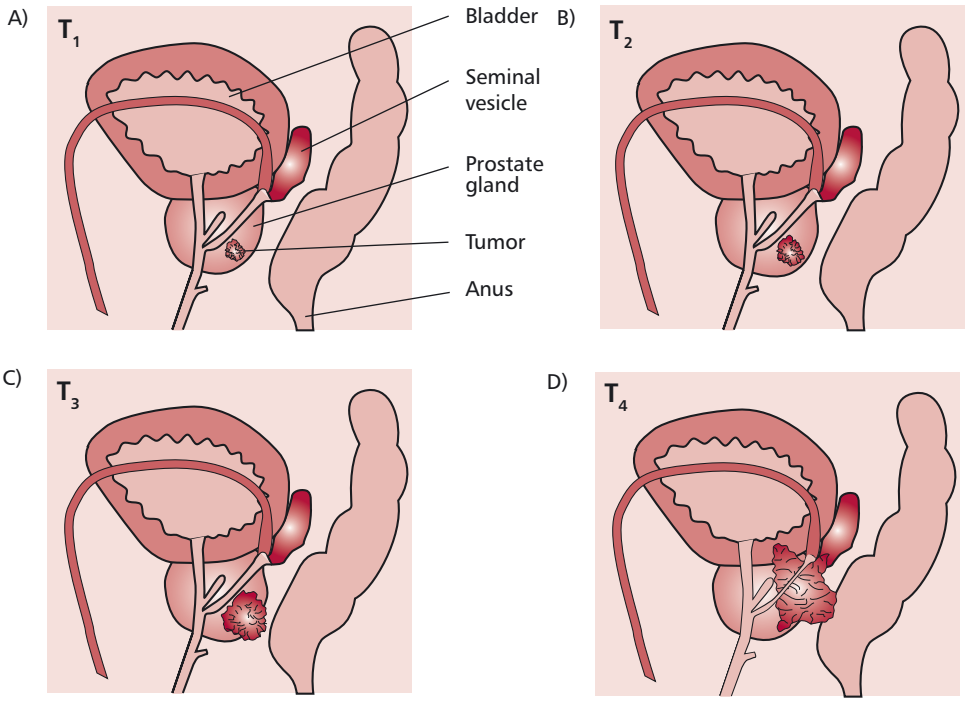


Figure 17.34 Diagrams (A–D) illustrating the four stages of prostate cancer.

be restricted to the more aggressive forms of the disease. Prostatectomy is the removal of the whole prostate gland and may result in impotence and incontinence.

External radiation therapy may be given following surgery to ensure that any remaining cancer cells are destroyed. Radiation therapy is also used as a first line of treatment and is an equally effective alternative to surgery. Therapeutic approaches include external beam and brachytherapy (*Section 17.6*). A form of external radiotherapy, known as conformational radiotherapy (CRT), allows the radiation beams to be shaped to match the shape of the prostate itself, which lowers the side effects caused by irradiation of the surrounding healthy tissue. Brachytherapy is delivered by the implantation of radioactive iodine 'seeds' or iridium wires in the prostate itself. If the cancer has spread to bone, radiation therapy using ^{89}Strontium, which is preferentially taken up by bone tissue, is given by intravenous injection.

Prostate cancer cells have receptors for the active form of testosterone and their growth requires a supply of testosterone from the testes. The aim of hormone therapy is to lower testosterone levels. Some of the drugs used are analogs of gonadotrophin releasing hormone (GnRH), examples being goserelin, leuprorelin and triptorelin. Goserelin is administered as a subcutaneous pellet while the others are injected subcutaneously or intramuscularly in liquid form. Other drugs used are antiandrogens, which block the interactions of hormone and receptor. The side effects of hormonal therapy include sexual impotence, flushes and sweating which may be reduced by intermittently stopping and starting the therapy.

The prognosis for men with prostate cancer is generally good, since this type of cancer usually occurs in older men and grows slowly.

COLORECTAL CANCER

Colorectal cancer, otherwise known as bowel cancer, is one of the three most common cancers in men and women, both in the UK and in the USA. In the UK there are about 35 000 new cases each year, with a slight majority occurring in men. Approximately 60% of new cases are cancers of the colon while the remainder have cancers of the rectum. In the USA there are roughly 135 000 cases each year, about 70% being colon cancers. The five-year survival rate for colorectal cancer is 50–60%. The vast majority of colorectal cancers are adenocarcinomas and this section will concentrate on these. The remainder fall into several groups as shown in *Table 17.10*.

Colorectal cancer	Description
Adenocarcinoma	95% of colorectal tumors, they arise from mucus-secreting cells in epithelium of GIT lining. Most produce mucin. Between 1 and 2% are **signet-ring** tumors where the intracellular mucus pushing nucleus to one side.
Squamous cell carcinoma	arise from epithelial cells of GIT lining.
Carcinoid tumor	rare, slow growing tumor of neuroendocrine origin.
Sarcoma	majority are leiomyosarcomas arising from smooth muscle in GIT wall.
Lymphomas	1% of colorectal cancers arising from lymphoid cells in GIT wall.

Table 17.10 Types of colorectal cancer

The risk factors for colorectal cancer include increasing age, a diet rich in fat and low in fiber, a history of inflammatory bowel disease and a hereditary predisposition. More than 80% are diagnosed in those aged over 60 years. A familial history of bowel cancer is also a strong risk factor as is the presence of **polyps**. A polyp is a benign tumor that arises from the epithelium of the GIT. Polyps range in size from a small bump to a lesion measuring 3 cm in diameter; most are asymptomatic.

Adenocarcinomas are known to originate from pre-existing polyps and the sequence of their development into a cancer is well documented. Individuals with familial adenomatous polyposis (FAP), a rare condition responsible for 1% of colorectal cancers, have a mutated form of the adenomatous polyposis coli (*APC)* gene. This gene encodes a protein that degrades β-catenin, which activates growth-promoting oncogenes such as *c-MYC*. Mutations in *APC* lead to the production of inactive β-catenin, hence oncogenes are continuously activated. Patients with FAP are almost certain to develop colorectal cancer in middle age and they are recommended to have their colon removed by

the age of 25 years. The development of colorectal cancer is also associated with both hypomethylation and hypermethylation of DNA and this has been detected at the polyp stage. Methylation of DNA is involved in switching genes off, hence hypomethylation can result in activation of oncogenes, whereas hypermethylation could lead to inactivation of tumor suppressor genes. Deletions in the long arm of chromosome 18 and in the short arm of chromosome 17 are also seen in colorectal cancers. Mutations in the *RAS* gene have been detected in cells in the feces of patients with colorectal cancer and it is possible that this may be used as the basis for a noninvasive diagnostic procedure.

The condition, hereditary nonpolyposis colorectal cancer (HNPCC) is associated with inherited mutations in a number of genes involved in DNA repair that also predispose an individual to colon cancer. Hereditary nonpolyposis colorectal cancer is estimated to cause between 2 and 5% of colorectal cancers and is linked to 40% of cases of colorectal cancer occurring in people below the age of 30 years. Other risk factors for colorectal cancer include being diabetic (*Chapter 7*) and being of Ashkenazi Jewish origin. This group also have a higher incidence of mutated *BRCA1* and *BRCA2* genes (*Section 17.5*) and are therefore also more likely to develop breast cancer. The genetic link to colorectal cancer has not been fully elucidated.

Signs, symptoms, diagnosis and staging of colorectal cancers

Patients with colorectal cancer may present with symptoms that include loss of weight, bleeding from the rectum and/or blood in the feces, anemia resulting in fatigue and breathlessness, changes in bowel habits, including increased diarrhea, and pain in the abdomen. The tumor may cause a bowel obstruction and if this occurs the patient suffers abdominal pain, nausea and constipation. An initial detection of a lump in the abdomen or rectum means that the patient must be referred for further specialist examination. Colonoscopy is used to examine the whole colon and to obtain a biopsy for further investigation. An alternative to colonoscopy is flexible sigmoidoscopy, an endoscopic technique which examines only the lower part of the colon and the rectum. The concentration of CEA (*Section 17.6*) in the blood can be measured although increased values are not entirely specific for cancer and a poorly differentiated tumor may not produce CEA. This measurement may, however, be useful for monitoring disease progress and treatment. Abdominal CT scans are helpful in diagnosis of metastatic spread to the lymph nodes and liver, and chest X-rays are routinely used to detect metastases in the lungs. Prognosis is poor for patients with metastatic spread to these two organs.

Several staging systems have been used for colorectal cancer. The Dukes system is shown in *Table 17.11* which also documents the proportion of patients who present at this stage, together with the survival rates at five or two years.

The TNM staging system is also used increasingly for colorectal cancers (*Figure 17.35*). T1, T2 and T4 are equivalent to Dukes A, B and D respectively. T3 describes the situation if the tumor has broken the outermost membrane of the GIT. The lymph nodes are classified as N0 if there are none containing cancer cells, N1 where between one and three nearby lymph nodes are involved, and N3, where there are cancer cells in four or more lymph nodes that are more than 3 cm from the main tumor, or where there are cancer cells in lymph nodes connected to the main blood vessels around the GIT.

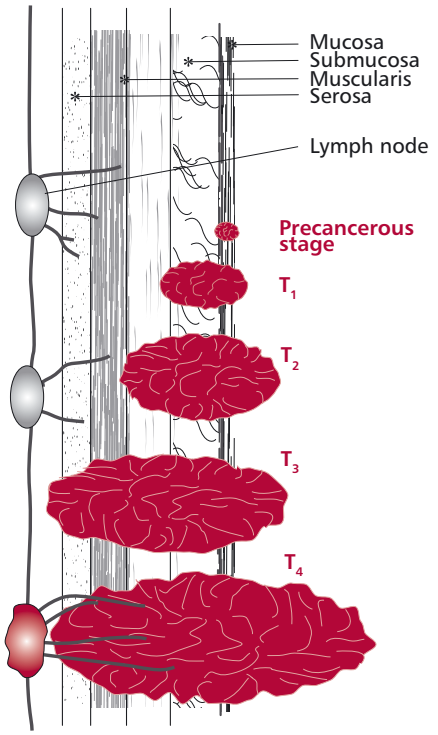


Figure 17.35 A diagram illustrating the four stages (TNM) of colorectal cancer.

Treatment of colorectal cancer

The usual treatment for colorectal cancer is surgery. Various procedures may be used but, if possible, a resection, in which the length of GIT containing the tumor is excised and the two cut ends are stapled together to reinstate the integrity of the GIT, will be performed. The advantage of resection is that

Dukes system	Description	Proportion of patients diagnosed/%	Prognosis (5-year survival as %)
Dukes A	cancer confined to innermost lining of colon/rectum	10	80
Dukes B	cancer grown into muscle layer of wall of colon/rectum	35	60–70
Dukes C	cancer spread to lymph nodes surrounding the colon/rectum	25	30–60
Dukes D	cancer has metastasized to other parts of the body	30	15 (survival at 2 years after diagnosis)

Table 17.11 Classification of colorectal cancers

the patient does not require a colostomy bag. Patients with rectal cancer may be given radiation treatment after surgery to reduce the risk of the tumor recurring locally. Radiation therapy may also be used in the palliative care of late stage metastatic cancer. Chemotherapy, 5-FU and leucovorin is sometimes offered postsurgery to patients with a Dukes B, and usually to those with Dukes C cancer. Chemotherapy of metastatic colorectal cancer uses 5-FU, leucovorin and irinotecan (CPT11). Combined oxaliplatin and 5FU treatment may also be used. Patients successfully treated for colorectal cancer should be regularly checked for several years after surgery to detect any recurrence of the tumor.

LEUKEMIAS

Leukemias are tumors of bone marrow cells that give rise to the blood cells and platelets (*Chapter 13*). Leukemias were historically classified according to the speed of onset and progression, with those of sudden onset and rapid progression termed acute leukemias, while those that develop slowly over months and years are called chronic leukemias. The current classification is based on specific typing of the blood cells, although the terms acute and chronic are still used. The main types of leukemias encountered clinically are acute myeloblastic and chronic myelogenous leukemias and acute lymphoblastic and chronic lymphocytic leukemias. Another rarer leukemia is hairy cell leukemia named according to the microscopic 'hair-like' appearance of the plasma membrane.

Most leukemias are characterized by symptoms such as excessive bleeding of the gums and nose, bruising, fatigue, breathlessness and increased susceptibility to infections. These are due to inadequate production of erythrocytes, platelets and lymphocytes owing to the abnormal proliferation of leukemic cells in the bone marrow. Blood and bone marrow films may show immature blast cells (*Figures 17.36*). Treatments for leukemia may involve chemotherapy, radiation therapy and stem cell transplantation (*Chapter 6*).

Chronic myelogenous leukemia

Chronic myelogenous leukemia (CML) is a rare disorder that affects approximately 500 people annually in the UK and accounts for between 7 and 15% of all leukemias. Patients are usually adults between the ages of 40 and 60 years. The disease is caused by malignant transformation of a myeloid stem cell which would normally give rise to the polymorphonuclear leukocytes, monocytes, basophils, erythrocytes and megakaryocytes. The clonal proliferation of a myeloid stem cell results in the accumulation of

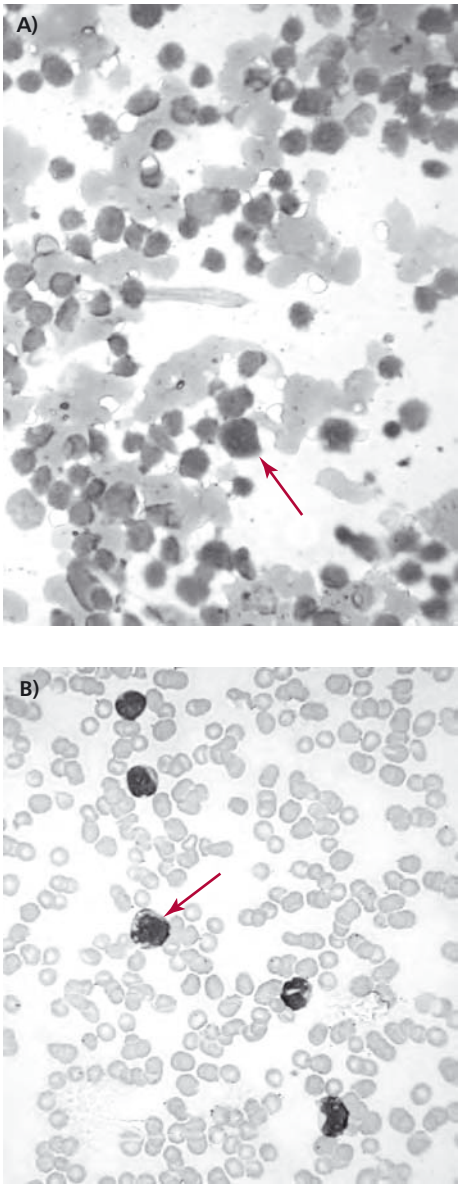


Figure 17.36 Blast cells, indicated by arrows, in (A) the bone marrow and (B) the blood of a patient with leukemia.

immature and mature myeloid cells within the bone marrow and spleen. Chronic myelogenous leukemia usually follows a clinical pattern in which there is a benign chronic phase, an accelerated phase and a blastic or blast crisis phase. During the chronic phase there are few signs and symptoms and many patients are asymptomatic. Patients may present with fatigue, anorexia and weight loss, and splenomegaly, with the condition being revealed by a routine blood count during the investigation of these symptoms. The blood count shows a leukocytosis, that is, an increased number of leukocytes, ranging from 10×10^9 to more than 500×10^9 cells dm^{-3}. A blood smear also shows large numbers of neutrophils and immature myelocytes. The Philadelphia chromosome is present in 95% of cases (*Section 17.4*). Splenomegaly may be present on examination. The presence of myeloblasts within a peripheral blood smear indicates a worsening of the disease and progression into the accelerated phase and the rapidly fatal blast crisis. This may take between three and five years from diagnosis.

Two major treatments are available for CML. The first is stem cell transplantation following radiation therapy to destroy the patient's own bone marrow (*Chapter 6*). The second is to use imanitib mesylate (Glivec) together with IFN-α. Imanitib mesylate is an inhibitor of tyrosine kinase that is administered orally. It is directed against the bcr-abl protein (*Section 17.5*) and is successful in inducing disease remission in approximately 90% of patients. However, the remainder are resistant, while up to 25% of patients also develop resistance during treatment. Chemotherapy with hydroxyurea may also be used. This is a temporary measure that reduces the leukocyte count by suppressing the division of the malignant cells. The effectiveness of treatment can be monitored by detecting the proportion of cells with the Philadelphia translocation.

Acute myeloid (myeloblastic) leukemia

Acute myeloid leukemia (AML) is a rare disease that affects approximately 2000 adults, mostly over the age of 60 years, and 100 children annually in the UK. The disease is characterized by the presence of immature myeloid cells, or myeloblasts, in the blood, due to clonal proliferation of an aberrant cell in the bone marrow. The cause of AML is unknown, though it has been linked to exposure to industrial solvents. There is no genetic link and cases are sporadic.

Acute myeloid leukemias are classified according to the type of cell which is involved, using the FAB (French–American–British) classification (*Table 17.12*).

Classification	Description
M0	AML with minimal myeloid differentiation
M1	AML without maturation
M2	AML with maturation
M3	acute promyelocytic leukemia
M4	acute myelomonocytic leukemia
M5	acute monocytic/monoblastic leukemia
M6	acute erythroleukemia
M7	acute megakaryoblastic leukemia

Table 17.12 FAB classification of acute myeloblastic leukemias

Patients present with anemia and bruising due to inadequate production of erythrocytes and platelets respectively. Poor platelet production is also associated with bleeding from the gums and nose. An inadequate production of appropriate leukocytes means that patients suffer repeated infections. Acute myeloid leukemia requires rapid diagnosis and immediate treatment. Chemotherapy is effective in bringing many patients into remission although high dose chemotherapy followed by a stem cell transplant may be required in some cases. Patients may require platelet transfusions before and during their treatment and erythropoietin may be given to treat the anemia. The use of the monoclonal antibody, gemtuzumab ozogamicin, directed at CD33 proteins present on the surfaces of the leukemic cells may be of some efficacy.

The prognosis for AML depends on the age at diagnosis. For adults under the age of 55 years, the five-year survival rate is between 40 and 60%, for those over 55 years it is unfortunately only 20%.

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia, affecting mostly those aged over 60 years. It is characterized by the clonal proliferation of lymphoid stem cells. However, the disease is slow growing and many patients are asymptomatic in the early stages. Signs and symptoms include frequent infections, anemia, bleeding and bruising. The spleen and the lymph nodes in the neck, axillae and groin may be swollen due to the accumulation of abnormal cells. The cause of CLL is unknown although in a minority of cases the disease may be familial. A diagnosis of CLL is by examination of blood and bone marrow. A lymph node biopsy may also be taken for histological examination. The disease is described as Stage A, B or C according to the degree of lymph node involvement. Stage C patients have enlarged lymph nodes in three or more areas and a low erythrocyte and/or platelet count. Patients with Stage A, with little or no lymph node enlargement may not need treatment. Patients with Stages B and C may be brought into remission with chemotherapy. Treatment is usually successful in maintaining remissions for several years.

Hairy cell leukemia is a rare form of CLL which occurs in people between 40 and 60 years of age. It constitutes 2–5% of leukemias. The leukemic cell is a B lymphocyte and is characterized by cells with outgrowths or projections which give the disorder its name (*Figure 17.37*) although the cause of the pathology is not known. Patients present with symptoms of breathlessness, weakness, weight loss and infections. There may also be splenomegaly. Diagnosis is by examination of blood smears and demonstration of splenomegaly on examination. Histological examination of a bone marrow specimen is also undertaken.

Treatment of hairy cell leukemia is by chemotherapy, using cytotoxic drugs. Interferon α has also been used to treat this disorder. The prognosis for hairy cell leukemia is good. The leukemia is slow growing and chemotherapy may only be needed after regular monitoring of cell counts reveals the count of abnormal cells is rising and if the patient presents with symptoms.

Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is a rare disorder that occurs most frequently in children under the age of 15 years although it does affect around 600 adults annually in the UK, mostly between the ages of 15 and 25 and those over 75 years of age. The cause of ALL is unknown. The disease is characterized by a clonal proliferation of a lymphoid stem cell, leading to increased numbers of lymphoblasts in the blood. As with other leukemias, patients may present with unusual bleeding of the gums and nose, bruising, anemia, aching

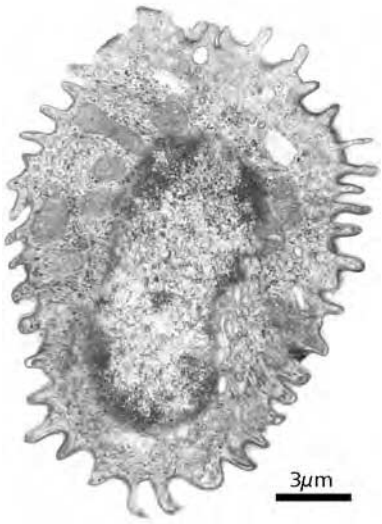


Figure 17.37 An electron micrograph of a single leukemic cell from a patient with hairy cell leukemia. Note the numerous extensions of the plasma membrane that give the condition its name.

joints and bones and a general feeling of malaise. Diagnosis is achieved by microscopic examination of bone marrow taken from the pelvis or sternum. A lumbar puncture may be used to obtain a sample of cerebrospinal fluid, to detect the presence of leukemic cells.

Acute lymphoblastic leukemia is classified into three types according to the FAB classification. These are L1ALL, in which the lymphoblasts resemble mature lymphocytes, with L2ALL and L3ALL showing increasingly immature forms of lymphoblasts. The disease may also be classified according to whether the leukemic cells are T cells or B cells, or pre-B cells, which are immature forms. A diagnosis of these forms involves histological examination and immunofluorescence testing of cell surface characteristics, with analysis by flow cytometry (*Box 6.1* and *Chapter 4*). A proportion of ALL patients also have the Philadelphia chromosome, which can be shown by karyotyping.

The treatment for ALL involves chemotherapy and this achieves remission in 80% of patients. Chemotherapy may also require intrathecal injection of chemotherapeutic agents (*Section 17.7*) to destroy leukemic cells in the cerebrospinal fluid. Steroids, such as dexamethasone, may be combined with cytotoxic drugs and imanitib may also be used. Radiation therapy to the brain and the testes in men may also be required to prevent recurrence. When patients are at high risk of relapse, a stem cell transplant may be required.

The survival rates for ALL depend on the age at which it is diagnosed. Children with ALL have a five-year survival rate of between 65 and 75%, while for adults it is only 20–35%.

CASE STUDY 17.1

Chris, a 56-year-old man, recently noticed that he needed to urinate more frequently, especially during the night. Also, urination was painful. He visited his doctor where a rectal examination showed his prostate gland to be enlarged and smooth. A blood sample was taken for a PSA test. The results showed the level of PSA in his blood to be 5.3 ng cm^{-3}.

Questions

(a) What is the likely diagnosis for Chris?

(b) What would be the recommended treatment?

CASE STUDY 17.2

Rebecca is a 55-year-old woman. About four weeks ago she developed a bad cold and cough. While the cold cleared up, the cough has remained and has become more painful. During the last week she was alarmed to find that she was coughing blood into her handkerchief, especially first thing in the morning. Rebecca gave up smoking about two years ago, but was previously a smoker of 20 cigarettes a day, starting from the age of 23 years. Her husband also smokes. Rebecca visited her physician who referred her to a consultant. The consultant saw Rebecca two weeks later and she had a full examination, including a chest X-ray.

Questions

(a) What clinical findings might the physician be expecting to see?

(b) What is the risk of Rebecca having lung cancer if she is a nonsmoker?

CASE STUDY 17.3

Giles is a 14-year-old boy who, until recently, was a normal adolescent who loved sports, especially soccer. During the last few weeks, however, Giles has been feeling unwell. He has only played soccer twice in the last four weeks and, each time, he felt too tired during the first half to carry on for the whole match. Giles' mother noticed her son's tiredness and worried about the number of coughs and colds he suffered. However, when she noticed a number of large bruises on his legs and torso, she decided to take him to see his doctor who took a sample of blood for a full blood and platelet count. The blood count indicated a leukocytosis, with numerous blast cells present. Platelet numbers were reduced and there were indications of anemia.

Questions

(a) What disorders might be suspected?

(b) What further tests would confirm or refute your suspicions?

17.9 SUMMARY

Cancer is a group of diseases in which cells escape from the usual regulatory factors controlling cell division and proliferate to form tumors. Cells from tumors may break free and move through the blood and lymph to establish tumors at distant sites. Cancer is ultimately caused by successive mutations in the DNA that confer a selective advantage to the cancer cells. Examples of genes which, when mutated, may give rise to cancers include cellular proto-oncogenes and tumor suppressor genes. Mutations may be caused by chemical carcinogens or radiation, by oncogenic viruses or by intrinsic failures of DNA repair mechanisms. Some gene mutations that predispose to cancer are inherited. Examples include mutated forms of the *BRCA1* and *BRCA2* genes which predispose women to cancers of the breast and/or ovaries.

Diagnosis of cancer depends on the location and symptoms produced by the tumor. A whole battery of diagnostic procedures may be used, including tumor imaging, histological examination of tumor biopsies and immunoassays for tumor associated markers. Treatments for cancer include chemotherapy, radiation therapy and immunotherapy. In addition, hormone therapy may be useful for cancers of the prostate and breast.

QUESTIONS

1. Which of the following is the odd one out?
   a) Epstein-Barr virus;
   b) HIV;
   c) Kaposi's virus;
   d) human papilloma virus;
   e) human T-cell leukemia virus.

2. Which of the following statements is incorrect?
   a) A benign tumor does not metastasize.
   b) Oncogenes may be found in certain viruses.
   c) Tumor suppressor genes control cell division.
   d) Cancer may be treated with cytotoxic drugs.
   e) Leukemic cells originate in the blood.

3. Which of the following are the four most common tumor sites in adults in the UK?

   a) Lung, breast, colorectum and bone marrow;
   b) Breast, lung, colorectum and prostate;
   c) Lung, breast, stomach and prostate;
   d) Brain, lung, breast and bone marrow;
   e) Stomach, lung, skin and breast.

4. Arrange the two following lists into their most appropriate pairings.

Carcinoma	*BCR-ABL*
Metastasis	*TP53*
Oncogene	myeloblastic leukemias
Tumor suppressor gene	Hodgkin's lymphoma
Breast cancer	xeroderma pigmentosum
Li-Fraumeni syndrome	secondary tumors
Tyrosine kinase	*EMSY*
FAB	epithelia
Ultraviolet light	*E2F3*
Epstein-Barr virus	*CHK2*

5. Indicate whether the following statements are **TRUE** or are **FALSE**.

   a) Cachexia is defined as an unexplained loss of 2 kg of body weight.
   b) A viral equivalent of an abnormal human gene that is associated with cancer is denoted by the prefix *v-*.
   c) Cigarette smoke contains benzo[a]pyrene, which is a direct acting carcinogen.
   d) The use of a cryostat allows for a rapid histological examination of biopsy material from a suspected cancer.
   e) Cells undergoing mitosis are at their most resistant to radiation damage.
   f) Methotrexate is an antagonist to folic acid synthesis.
   g) Cyclophosphamide and 6-TA are used in the treatment of breast cancer.
   h) Vincristine, obtainable from *Colchicum officinale*, is used to treat leukemias.
   i) Coley's toxin contains killed Mycobacteria that stimulate the immune system.
   j) Hairy cell leukemia is the name of a rare form of ALL.

6. Write a 1500 word essay on the diagnosis and treatment of cancer.

FURTHER READING

Bhurani, D and Gottlieb, D (2004) The chronic leukaemias http://www.australiandoctor.com.au

Caldas, C (1998) Molecular assessment of cancer. *BMJ* **316:** 1360–1363.

Cooperberg, MR, Moul, JW and Carrol, PR (2005) The changing face of prostate cancer. *J. Clin. Oncol.* **10:** 8146–8151.

Doll, R (2000) Smoking and Lung Cancer. *Am. J. Crit. Care Med.* **162:** 4–6.

Donaldson, MS (2004) Nutrition and cancer: a review of the evidence for an anti-cancer diet. *Nutr. J.* **3:** 19–40.

El-Deiry, WS (2005) Colon cancer, adenocarcinoma. http://www.emedicine.com

Flaitz, CM and Hicks, MJ (1998) Molecular Piracy: the viral link to carcinogenesis. *Oral Oncol.* **34:** 448–453.

Futreal, PA, Coin, L, Marshall, M, Down, T, Hubbard, T, Wooster, R, Rahman, N and Stratton, MR (2004) A census of human cancer genes. *Nat. Rev. Cancer* **4**: 177–183.

Garland, CF, Garland, FC, Gorham, ED, Lipkin, M, Newmark, H, Sharif, BM and Holick, MF (2006) The role of vitamin D in cancer prevention. *Am. J. Public Health* **96:** 252–261.

Giordano, SH, Cohen, DS, Buzdar, AU, Perkins, G and Hortobagyi, GN. (2004) Breast cancer in men: A population-based study. *Cancer* **101:** 51–57.

Hoffbrand AV, Petit JE and Moss PAH (2001) *Essential Hematology.* 4th edn. Blackwell Science, Malden, MA.

Horig, H, Medina, FA, Conkright, WA and Kaufman, HL (2000) Strategies for cancer therapy using carcinoembryonic antigen vaccines. *Exp. Rev. Molec. Med.* **2000**: 1–24.

Jones, GR (2003) Li-Fraumeni syndrome. http://www.emedicine.com

King, JBR and Robins, M (2006) *Cancer Biology.* Prentice-Hall Ltd, Harlow, UK.

Latonen, L and Laiho, M (2005) Cellular UV damage responses-Functions of tumor suppressor p53. *Biochim. Biophys. Acta* **1755:** 71–89.

Liesner, RJ and Goldstone, AH (1997) ABC of clinical haematology: the acute leukaemias. *BMJ* **314:** 733–736.

Office for National Statistics (2005) Cancer statistics registration: Registrations of cancer diagnosed in 2002, England. Crown Copyright 2005. Also at http://www.statistics.gov.uk

Radtke, F and Clevers, H (2005) Self-renewal and cancer to the gut: Two sides of a coin. *Science* **307:** 1904–1909.

Ries, LAG, Eisner, MP, Kosary, CL, Hankey, BF, Miller, BA, Clegg, L, Mariotto, A, Feuer, EJ and Edwards, BK (eds). *SEER Cancer Statistics Review, 1975–2002*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER data submission, posted to the SEER web site 2005.

Tisdale, MJ (2005) Molecular pathways leading to cancer cachexia. *Physiology* **20:** 340–348.

Turnbull, C and Hodgson, S (2005) Genetic predisposition to cancer. *Clin. Med.* **5:** 491–498.

Uauy, R and Solomons, N (2005) Diet, nutrition and the life-course approach to cancer prevention. *J. Nutr.* **135:** 2934S–2945S.

Various authors (2001) *Nature* **411:** 335–396. Contains a series of articles on cancer.

von Meyenfeldt, M (2005) Cancer-associated malnutrition: an introduction. *Eur. J. Oncol. Nurs.* **9:** S33–S38.

Wallis, G (1999) *The Genetic Basis of Human Disease*. The Biochemical Society, London. http://www.biochemistry.org/

Yuspa, SH (2000) Overview of carcinogenesis: past, present and future. *Carcinogenesis* **21:** 341–344.

Useful web sites:

The National Institute for Clinical Excellence (NICE) publishes its guidelines for treatment of patients at NICE guidelines www.nice.org.uk

http://www.cancerhelp.org.uk This is an excellent website with lots of useful information on many different types of cancer.

http://www.cancerbacup.org.uk Another excellent website with information on cancer.