Bio Factsheet

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Biological Basis of Cancer

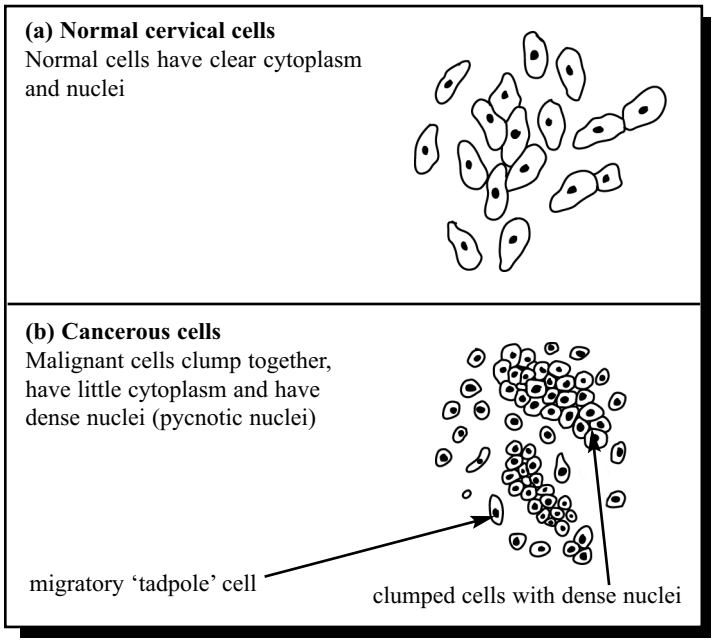
This Factsheet describes the causes, characteristics, diagnosis and treatment of cancer.

There are over 200 different forms of cancer, All have a similar origin: the uncontrolled replication of cells, resulting in the formation of tumours.

Cancers account for about 25% of all deaths in the UK, and are the second biggest killer after cardiovascular disease. In males, lung cancer is the most common, whereas in females it is breast cancer.

Remember - epidemiology *is the study of the patterns of disease and the various factors that affect the spread of disease within populations*

Fig 1. Cervical smears, showing normal cells and malignant cells.



Exam Hint: *Learn the details of cell division because this will help you to answer longer essay questions.*

Tumour Development

The tumours arise from problems with the mechanisms responsible for the control of cell division. The problems may be due to:

- mutations;
- abnormal activation of the genes involved (if this occurs the genes are referred to as **oncogenes**). The genes may be activated by carcinogens. A **carcinogen** is any agent that can cause the development of cancer.

If these abnormal cells are not recognised by the immune system and suppressed, they will multiply uncontrollably, resulting in the formation of a bundle of identical cells, called the **primary tumour**. Tumour cells can break away and spread to other parts of the body by **two** methods:

- the tumour cells become mobile by amoeboid action (then called 'tadpole cells') and can migrate into nearby areas.
- the tumour cells can be transported in the bloodstream and the lymphatic system.

The process of invasion of other body tissues by cells from the primary tumour is called **metastasis**. This gives rise to **secondary tumours** or **metastases** in organs such as the liver, adrenal glands and the brain. If the tumour cells are transported in the blood the secondary tumour is likely to be distant from the primary tumour, however if the transport system is the lymph, it is most likely to occur in a lymph node close to the original tumour.

Some tumours that form do not spread and are referred to as benign, and are usually harmless. Tumours that spread, thus causing the development of secondary tumours, (which can also spread), are classed as malignant and can result in serious illness or death.

Exam Hint: *A common (and simple) mistake is to confuse benign and malignant tumours.*

Fig 2. Diagram of development and spread of secondary tumours.

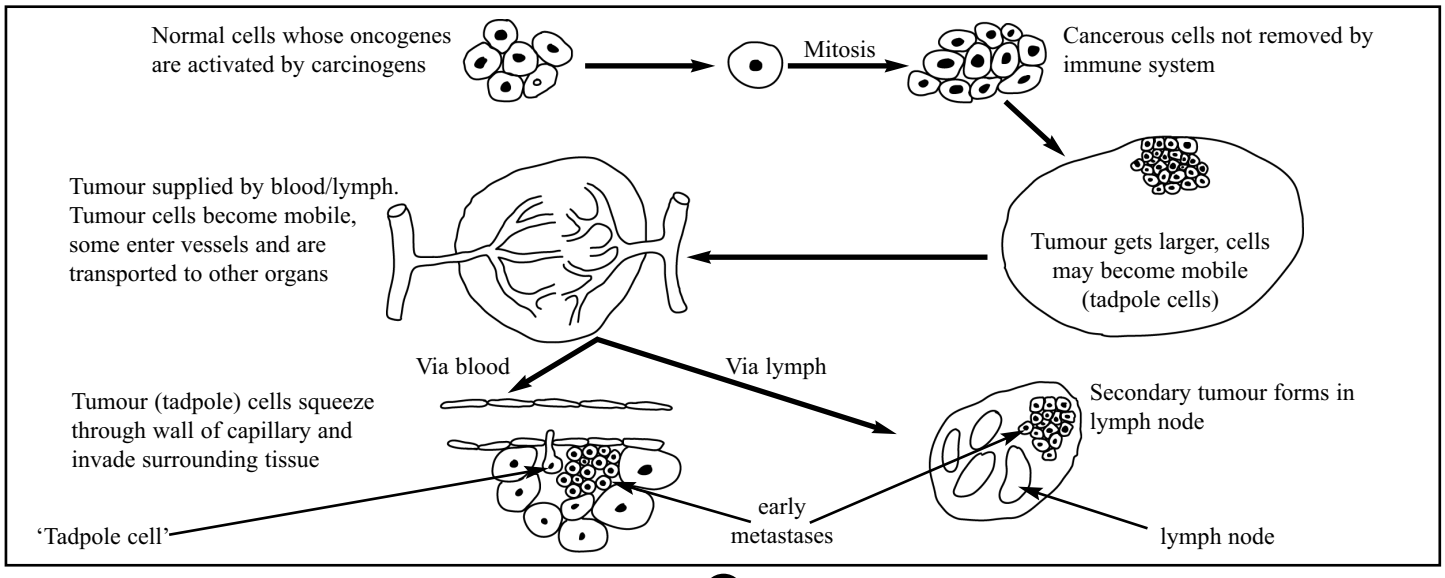


Table 1 Carcinogenic agents.

Carcinogenic agents	Relevant information	Associated cancers
Ultraviolet light (non-ionising radiation). Wavelengths between 250 to 270 nm are the most dangerous and are found in bright sunshine, particularly since ozone has become depleted in the upper atmosphere.	UV-light energy is absorbed by the nitrogenous bases in DNA and results in the formation of thymine dimers. These couple across the DNA instead of thymine coupling to adenine, causing the DNA to develop abnormal bulges. Most people have an enzyme that in light repairs the DNA. Some people have a gene mutation which causes the repair enzyme to be damaged, and this allows the development of skin cancers. UV-light cannot penetrate further than the epidermis.	Skin cancer (Xeroderma pigmentosum).
X-rays, α, β, γ – rays, cosmic rays. (ionising radiations)	Alpha-rays are helium nuclei, beta-rays are electrons or positrons, gamma-rays are electromagnetic radiation. They all come from radioactive sources. X-rays and gamma-rays act by: • directly breaking DNA and RNA into short lengths. • splitting water into reactive ionised fragments which damage DNA indirectly.	Lung, breast, bone marrow cancers.
Mutagenic chemicals Polycyclic hydrocarbons nitrosamines, aromatic amines.	Mustard gas adds a methyl or similar alkyl group to guanine altering its ability to base pair. This causes the release of guanine from DNA so that the position occupied by guanine can then be filled by another base. Many other chemicals are base analogues which have similar structures to the normal bases and so can become incorporated into the DNA in place of them during replication. An example is 5-bromouracil. Other mutagenic chemicals include dioxin, colchicine, caffeine, some pesticides and several tobacco products. Polycyclic hydrocarbons are found in soot and tobacco smoke.	Environmentally caused cancers, such as lung cancer (linked to polycyclic hydrocarbons).
Viruses HIV-1, papilloma viruses, Epstein-Barr virus.	Some viruses can contain genes that when inserted into the host cells DNA become oncogenes. For example, when a retrovirus such as **HIV-1**, (an RNA virus), invades an animal cell it uses reverse transcriptase to convert the viral RNA into copy DNA. The cDNA can then be inserted into the host's genome altering the host's cell division genes and switching them on, causing the cell to become malignant. DNA viruses such as the **Epstein-Barr virus** contain their own oncogenes, which when inserted into the host's DNA cause uncontrolled cell division.	Cervical cancer (linked to papilloma viruses).

Causes of cancer

The incidence of some cancers increases with age, for example, cancer of the gut, skin and urinary tract. Some cancers have been shown to have a strong **genetic predisposition**, such as breast cancer and ovarian cancer. The genes involved may be oncogenes, or genes that stop the immune system from recognising and attacking cancer cells therefore allowing the development of tumours. Also, carcinogens *(see Table 1)* can increase the chance of tumour formation.

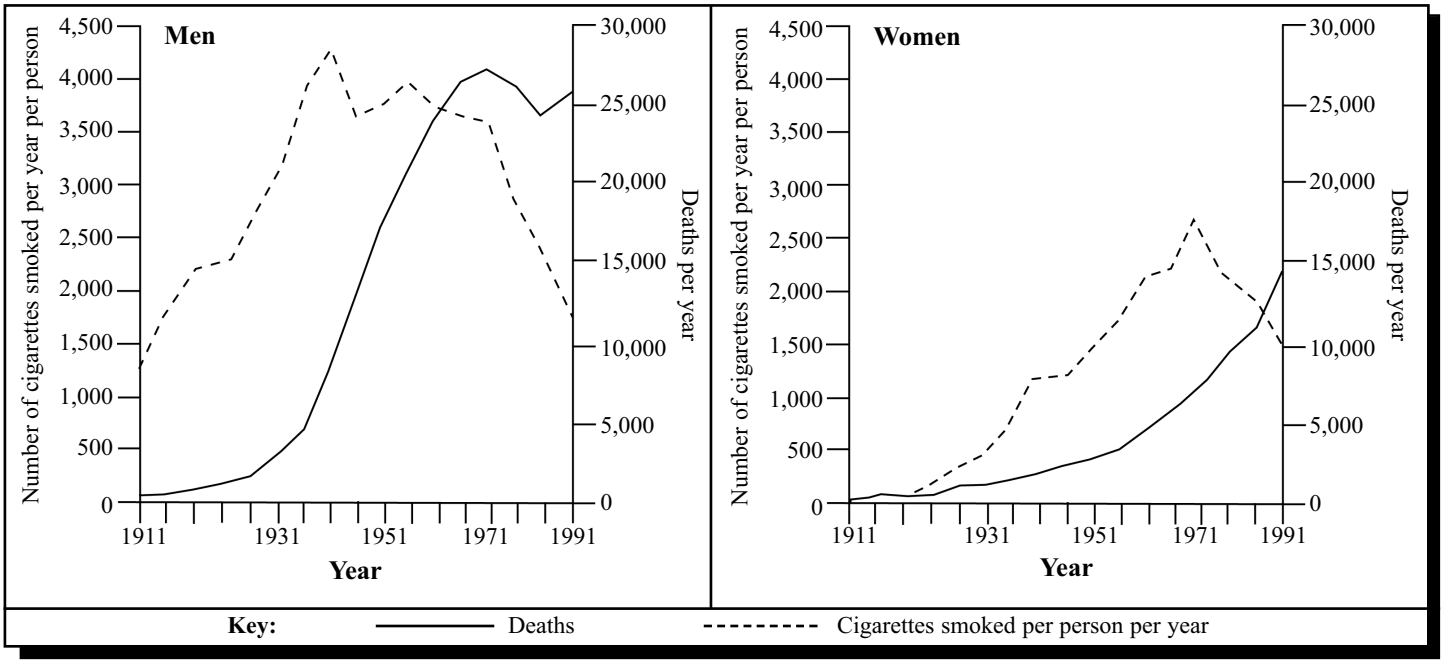
It is likely that the formation of a malignant cancer cell is caused by several factors operating over a number of years, rather than being caused by a single factor alone.

Lung Cancer

The link between lung cancer and smoking was first identified by epidemiological studies. By studying and comparing graphs *(Fig. 2)* showing the number of cigarettes smoked and the number of deaths from lung cancer it was possible to see the first evidence of an association.

Practice exam technique: *Study the graphs and practise summarising the trends shown. If a question just asks you to* ***describe*** *the data, then refer to the trends shown and include values, but do not try to explain the data, because marks will not be available for an explanation. If you are asked to* ***compare*** *the data for males and females you must refer to both for each comparison you make.*

Fig 2. Smoking and lung cancer



There is a clear correlation showing that as smoking became more prevalent, due to changing fashions, so the number of deaths from lung cancer increased. While these studies weren't conclusive, when they were repeated for other possible causes, such as atmospheric pollution, no such correlations were found.

Since these studies, experimental evidence has shown a direct causative link between the chemicals contained in cigarette smoke and lung cancer. It has been shown that the tar present in cigarettes contains polycyclic hydrocarbon carcinogens, such as **benzyprene** and **co-carcinogens**. A co-carcinogen is a substance that increases the chance that a carcinogen will cause changes in DNA

Throughout both the developed and developing world, the number of people smoking is still very high, despite the evidence of the risk to health, not just of developing lung cancer, but also of developing coronary heart disease, and of the increased risk of strokes. This has lead to a huge strain on the health service, both financially and physically, resulting in calls to prioritise treatment, with smokers being treated after non-smokers, also the withholding of certain treatments, (such as heart bypass surgery), if the patient is still smoking.

Smoking and Lung Cancer

- The risk of developing lung cancer will be higher if the smoker:
  - Inhales
  - Smokes high tar cigarettes
  - Smokes for a long period of time
  - Smokes a large number of cigarettes a day
  - Starts smoking from a young age
  - Smokes cigarettes without filters
- If smoking is stopped the risk decreases, but it takes over ten years for the risk to return to the same level as a non-smoker
- One-third of all cancer-related deaths are a direct result of cigarette smoking
- Lung cancer is responsible for 25% of all deaths of smokers
- Smokers are nearly 20 times more likely to develop lung cancer than non-smokers

Skin Cancers/Melanoma

Similar to lung cancer, there has been a link observed between increasing levels of UV-radiation in sunlight and skin cancer. Over the years UV levels have been increasing, due to the depletion of the ozone layer caused by polluting CFCs used in refrigerators, aerosol propellants and foam expanders. The increase in UV-light intensity is linked directly to an increased incidence of skin cancer, although this trend is being reversed to some extent by increased public awareness about pollution and use of sun lotions which 'filter out' the UV-light.

The skin pigment **melanin** provides some protection by absorbing the radiation. Melanoma is a highly malignant tumour, which often forms secondary tumours in the brain, resulting in death.

Exam Hint: *The topic of UV-radiation and skin cancer often appears in questions relating to pollution, particularly in synoptic questions and essays.*

Diagnosis of cancer

The sooner cancer is diagnosed the better the prognosis (likelihood of a cure), therefore a lot of research has focused on this aspect of cancer. As a result there are a range of techniques available, ranging from **X-raying** the possible affected area such as the breast (mammography) or assessing the area using imaging techniques such as **ultrasound scanning**, **computerised tomography (CT)** and **magnetic resonance imaging (MRI)**. The success of these techniques relies on the presence of a tumour that is large enough to be detected. Others techniques involve taking samples of body fluids, such as blood, and testing them biochemically for abnormal products of cancer cells or histologically for abnormal leucocytes in leukaemias.

More recently there have been advances using **monoclonal antibodies**, which allow the diagnosis of cancers much earlier than the other techniques. The advantage of using monoclonal antibodies is their specific binding to antigens on the cancer cells in question. For example, leukaemias and lymphomas are both cancers of white blood cells, which are hard to distinguish between. The use of monoclonal antibodies allows the recognition of the different antigens on these cells. The monoclonal antibodies are tagged with harmless **radioactive tracers (radionuclides)** which emit gamma-rays. As the tracer collects at clumps of cancer cells it can be visualised by gamma scanning (not all types of gamma-ray are dangerous). A three-dimensional image of the tumour and its position can be built up and this enables radiotherapy treatment to be accurately directed. A radionuclide in common use is technetium (^{99}Tc). For thyroid studies, radionuclides of iodine (^{125}I and ^{131}I) are used.

Diagnostic techniques like this should enable early diagnosis of common cancers, such as breast and colon cancer, without taking samples of body fluids.

Treatment

Once cancer is diagnosed, the choice of treatment depends on the site, nature and extent of the tumours. The main treatments are:

- **Surgery** to remove the tumour
- **Radiotherapy** of the affected area using X-rays or γ-rays to kill tumour cells. Some tumours respond poorly to this type of treatment if they have low internal oxygen levels. Because radiation has to be precisely directed to the cancer, radiotherapy can only be used for cancers that are in discrete tumour form and cannot be used against dispersed cancer cells.
- **Chemotherapy** of the whole body using chemicals which kill dividing cells, including normal and tumour cells.
- **Chemotherapy** using drugs such as **Tamoxifen**, which reduces the risk of developing of breast tumours by reducing oestrogen levels as high oestrogen levels can stimulate the growth of breast tumours.

A natural means of defence against cancer is the immune system, and research is being directed towards finding ways to stimulate immune reactions, for example, by using **interferons** and **interleukins** produced by genetically modified bacteria.

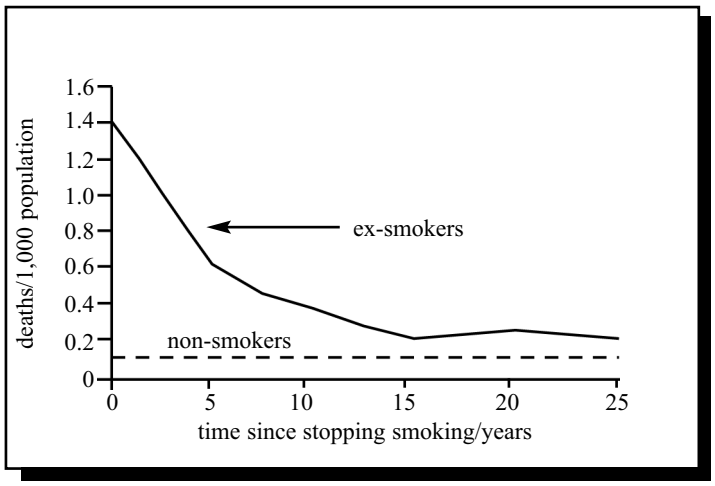
Radiotherapy and chemotherapy unfortunately kill some normal dividing body cells as well as cancer cells and so treatment with these methods has unpleasant side effects, for example, hair loss and damage to the gut lining. Fortunately the cancer cells are much more sensitive to the treatments than normal cells and so treatment is still possible.

The use of monoclonal antibodies in diagnosis has already been discussed, but they also have a potential role in the treatment of cancers. Anti-cancer drugs can be attached to the antibody and thus delivered to the desired site; these are the so-called **magic bullets**.

Another technique is to tag monoclonal antibodies with an enzyme that converts the inactive form (**prodrug**) of an anti-cancer drug into an active form. The prodrug is then administered in high doses, but will only be activated at cancer cells by the presence of the enzyme, thus killing them, while not having any effect on non-cancerous cells. This technique is called **ADEPT (Antibody Direct Enzyme Prodrug Therapy)**.

Practice Questions

1. The graph shows the death rate per thousand of the population from lung cancer of non-smokers and ex-smokers.



(a) (i) Describe the pattern of the curve for ex-smokers. 3

(ii) Suggest two reasons why it takes so many years for the number of deaths to decrease to the lowest point. 2

There are approximately 5.9 million new cancer cases in the world each year and 1 in 10 deaths is caused by cancer. The table below shows some differences between developed and developing countries:

	Developed countries	Developing countries
Number of new cancer cases per year	2.9 million	3.0 million
Number of deaths due to cancer per year	1 in 5	1 in 16
Life expectancy	70+ years	50 – 60 years
Age range with highest incidence of cancer	60 + years	30 – 40 years

(b) Suggest an explanation for the difference between developed (industrialised) countries and developing countries in:

(i) the age range with the greatest incidence of cancer. 2

(ii) the deaths per year due to cancer. 2

Total 9

2. Outline the sequence of events in the formation of a secondary tumour. Total 10

3. (a) (i) Define the term 'carcinogen'. 1

(ii) Name a chemical carcinogen and say which cancer it is implicated to. 2

(iii) Name a non-ionising radiation and say which cancer it is implicated to. 2

(b) 'Ionising radiations can be used for diagnosis and for treatment of cancer'. Explain this statement. 5

Total 10

Answers

1. (a) (i) rapid fall of deaths per thousand from1.4 to 0.6/number of deaths (more than) halve in first five years;
decreases more slowly in next 10 years from 0.6 to 0.2;
levels off at around 0.2 deaths per thousand; 3

(ii) carcinogens/deposits/ named deposit take time to remove from lungs;
cancers already present due to exposure to carcinogens before stopping smoking;
lung damage due to smoking takes long time to repair; max 2

(b) (i) more people smoke in developing countries;
fewer controls on industrial emissions in developing countries; 2

(ii) in developing countries people more likely to die of communicable diseases;
developed countries people live longer so more likely to die of cancer;
in developed countries better diagnosis of cancer as cause of death; max 2

2. oncogenes are activated by carcinogens;
cancerous cell does not respond to signals from other cells;
mitosis occurs;
cancerous cells are not removed by the immune system;
rapid mitosis occurs;
tumour gets bigger, cells change their appearance and can be detected under a microscope;
ref to migratory cells/tadpole cells;
tumour supplied with blood and lymph vessels;
tumour cells spread in these vessels to other parts of the body;
ref to metastasis/cells invade other tissues;
secondary cancers form throughout the body; max 10

3. (a) (i) A carcinogen is an agent which can cause the development of cancer; 1

(ii) benzyprene/polycyclic hydrocarbons;
lung cancer; 2

(iii) ultra-violet light;
skin cancer/melanoma/xeroderma pigmentosum; 2

(b) ref to radionuclides/ technetium /$^{99}Tc^{m}$ /iodine /^{125}I / ^{131}I;
taken up preferentially by cancer cells/attached to monoclonal antibodies which attach to cancer cells;
emit harmless/soft gamma rays which can be imaged by a gamma scanner/gamma camera;
tumours can be directly irradiated with damaging radiation;
harmful/hard X-rays or gamma-rays;
cancer cells more susceptible to radiation damage than normal cells; max 5

Acknowledgements
This Factsheet was researched and written by Fiona MacBain.
Bio Press. Unit 305B, The Big Peg, 120 Vyse Street, Birmingham B18 6NF