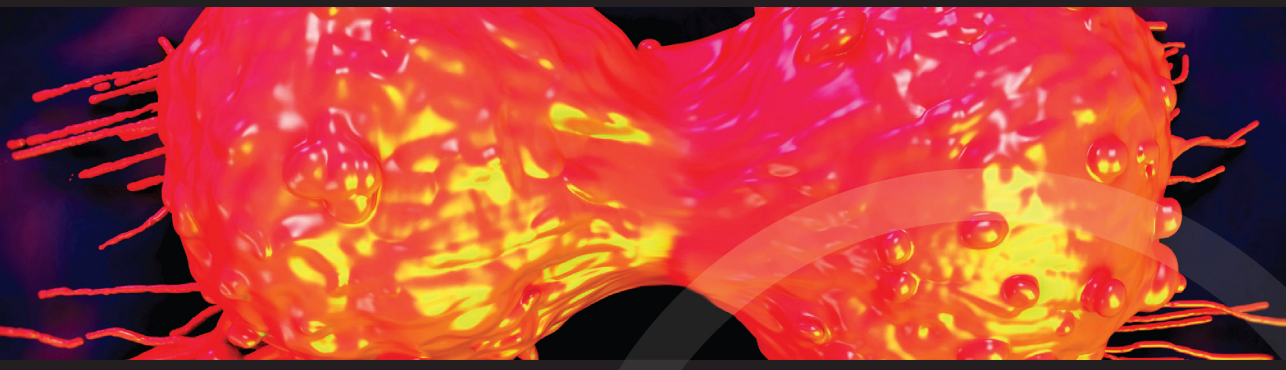
ONCOLOGY

Lecture Notes



Mark Bower
Jonathan Waxman

3rd Edition

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Oncology
Lecture Notes

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Third Edition

WILEY Blackwell

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Preface

Cancer is fabulous, and without a doubt, the most interesting and exciting of all the medical specialities. So you were right to buy this book.

When the authors of *Lecture Notes in Oncology* entered specialty training, we were told by our learned professors and mentors that we had made great career choices because oncology was at the forefront of the scientific advances in medicine.

At that time we were also told by these formidable men, and they were all men because there were no female oncology consultants in that era, that as a result of these advances incurable diseases were now curable. Four cancers were enumerated to encourage our interest in cancer; we were told that lymphoma, testicular cancer, choriocarcinoma and childhood leukaemia were curable. The number of patients cured was, of course, small but this at least was a start.

It is with joy that we admit that our teachers were right. It was a start that has led on to a galaxy of incredible treatments that have transformed the lives of patients. Cancer is indeed at the vanguard of modern medicine and changes in our understanding of how cancer cells work at the molecular level have been translated into a plethora of therapies that target these unique defects in cancer cells.

But it is not only these sparkling new treatments that are important in reducing cancer mortality. Screening strategies that detect and eliminate early cancers or their precursors have been developed and prophylactic vaccines that protect us from acquiring cancer-causing infections are available. As a consequence, death rates have fallen in many common cancers and the stigma of a cancer diagnosis has diminished.

Cancer has, of course, become politicized, as the reader of this preface might have noticed. We have the drugs, but in the United Kingdom at least dubious cost–benefit calculations mean that many of the drugs that would help our patients are branded as apparently unaffordable. We would urge the readers of this book to become involved politically and campaign for the right of patients to receive the treatment they need.

Mark Bower
Jonathan Waxman

About the companion website

Don't forget to visit the companion website for this book:

www.lecturenoteseries.com/oncology

There you will find valuable material designed to enhance your learning, including:

- Interactive multiple choice questions
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Part 1

Introduction to oncology

1

What is cancer?

Learning objectives

- ✓ List the histopathological features of cancer
- ✓ Classify cancers and recognize their nomenclature
- ✓ Explain the epidemiology of cancer

Cancer is not a single illness but a collection of many diseases that share common features. Cancer is widely viewed as a disease of genetic origin. It is caused by mutations of DNA and epigenetic changes that alter gene expression, which make a cell multiply uncontrollably. However, the description and definitions of cancer vary depending on the perspective as described below.

Epidemiological perspective

Cancer is a major cause of ill health. In 2011, in the United Kingdom, there were:

- 434,115 new cases of cancer
- 159,178 deaths from cancer

There are more than 200 different types of cancer, but four of them (breast, lung, colorectal and prostate) account for over half of all new cases (Table 1.1). Overall, it is estimated that one in three people will develop some form of cancer during their lifetime. In the period 1976–2009, the age-standardized incidence of cancer increased by 22% in men and 42% in women but have remained fairly constant over the last decade (Figures 1.1 and 1.2).

Cancer incidence refers to the number of new cancer cases arising in a specified period of time. Prevalence refers to the number of people who have received a diagnosis of cancer who are alive at any given time, some of whom will be cured and others will not. Therefore, prevalence reflects both the incidence of cancer and its associated survival pattern (Box 1.1). In 2010, approximately 3% of the population of the United Kingdom (around 2 million people) are alive having received a diagnosis of cancer. Over a million Britons are cancer survivors having lived more than 10 years since being diagnosed with cancer.

The epidemiology of cancer is littered with jargon, and some of the key terms are defined in Box 1.1.

Box 1.1 Understand the Geek-speak of epidemiology

Cancer incidence is the number of new cancer cases arising in a specified period of time.

Cancer prevalence is the number of people who have received a diagnosis of cancer who are alive at any given time, some of whom will be cured and others will not.

Cancer mortality is the number of deaths due to cancer in a specific time period and defined population.

Age-specific rates. To overcome problems of different population age structures, age-specific rates for an age range (usually 5–10 years) are published. For example, age-specific incidence rates of breast cancer in women aged 50–54 years.

Standardization is used to remove the effect of a variable that you are not interested in studying (often age or gender).

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Table 1.1 Most frequent cancers according to age and gender

Age	0–14 yr	15–24 yr	25–49 yr	50–74 yr	>74 yr
Male	Leukaemia Brain tumour Lymphoma	Testis Hodgkin lymphoma Leukaemia	Testis Melanoma Bowel	Prostate Lung Bowel	Prostate Lung Bowel
Female	Leukaemia Brain tumour Lymphoma	Hodgkin lymphoma Melanoma Ovary	Breast Melanoma Cervix	Breast Lung Bowel	Breast Bowel Lung

Age standardized rates. This corrects the crude rates to a "standardized population". The same "standard population" is used for all rates to allow comparisons.

Standardized ratios. Standardized incidence ratio (SIR) and mortality ratio (SMR) compare the age-specific rate in the study population with those of a control population.

Relative risk (also known as risk ratio) is the ratio of the risk of disease (e.g. lung cancer) amongst people exposed to a risk factor (e.g. smoking) to the risk amongst unexposed people (e.g. non-smokers). Data are calculated from cohort studies from which the incidence can be calculated.

Odds (as every gambler knows) is the ratio of the occurrence of an event to that of non-occurrence. If 20 out of every 100 smokers develop lung cancer, the odds are 20:80 or 1 in 4 (whilst the probability of developing lung cancer is 20/100 or 0.2).

Odds ratio compares the odds of an event in two different populations.

Sociological perspective

People living with cancer adopt a medically sanctioned form of deviant behaviour described in the 1950s by Talcott Parsons as "the sick role". In order to be excused from their usual duties and not to be considered responsible for their illness, patients are expected to seek professional advice and to adhere to treatments in order to get well. Medical practitioners are empowered to sanction their temporary absence from the workforce and family duties as well as to absolve them of blame. This behavioural model minimizes the impact of illness on the society and reduces the secondary gain that the patient benefits from as a consequence of their illness. However, as Ivan Illich pointed out, it also sets up physicians as agents of social control by medicalizing health and contributing to iatrogenic illness – "a medical nemesis". Of all the common medical diagnoses, cancer probably carries the greatest stigma and is associated with the most fear. The many different ways in which cancer affects people has been explored in literature (Table 1.2).

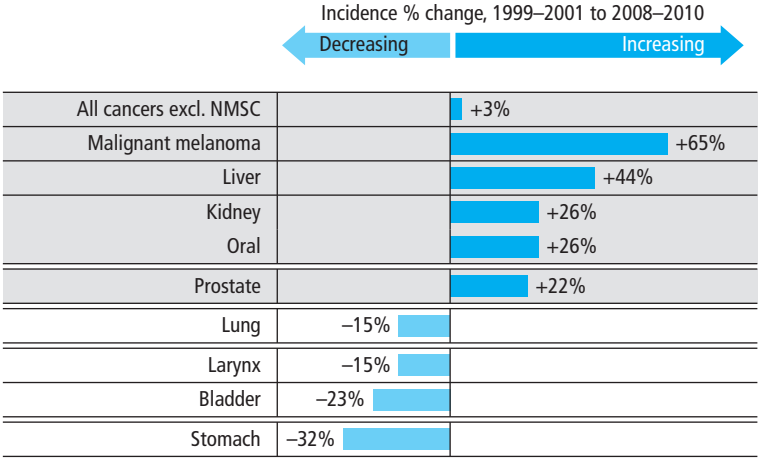


Figure 1.1 Fastest changing cancer incidences in men in the United Kingdom over the last decade. NMSC, non-melanoma skin cancer.

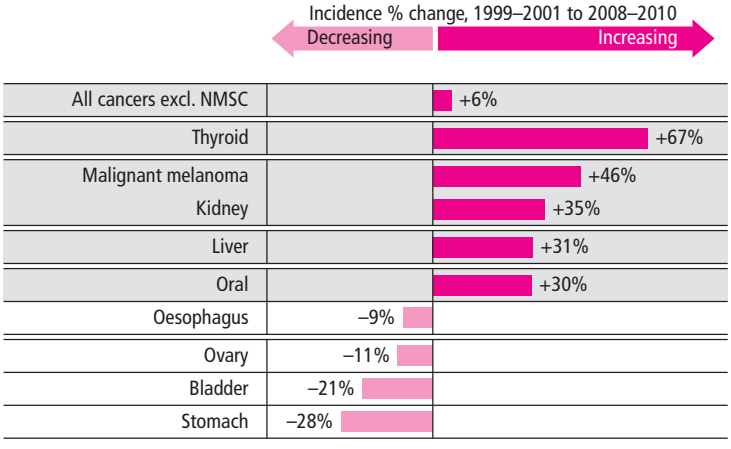


Figure 1.2 Fastest changing cancer incidences in women in the United Kingdom over the last decade.

Experimental perspective

In the laboratory, a number of characteristics define a cancer cell growing in culture. The four features listed below are used by scientists experimentally to confirm the malignant phenotype of cancer cells:

1. Cancer cells are clonal, having all derived from a single parent cell.
2. Cancer cells grow on soft agar in the absence of growth factors.
3. Cancer cells cross artificial membranes in culture systems.
4. Cancer cells form tumours if injected into immunodeficient strains of mice (Box 1.2).

Table 1.2 Tip top cancer books

	Title	Author
1	*Cancer Ward*	Alexander Solzhenitsyn
2	*A Very Easy Death*	Simone de Beauvoir
3	*Age of Iron*	J. M. Coetzee
4	*Cancer Vixen*	Marisa Acocella Marchetto
5	*One in Three*	Adam Wishart
6	*C: Because Cowards Get Cancer, Too*	John Diamond
7	*Before I Say Goodbye*	Ruth Picardie
8	*Illness as Metaphor*	Susan Sontag
9	*The Black Swan*	Thomas Mann
10	*Mom's Cancer*	Brian Fies
11	*Coda*	Simon Gray
12	*Cancer Tales*	Nell Dunn
13	*A Grief Observed*	C. S. Lewis

Box 1.2 Onco-mice

Mice have been used as a laboratory model in cancer research for a century. In the 1930s, Sir Ernest Kennaway showed that polycyclic aromatic hydrocarbons were carcinogenic by inducing skin cancers in mice. In 1969m the first inbred mice were developed that were essentially genetically identical except for gender. These strains allowed the transfer of cells and tissues between mice without rejection, as they are syngeneic (genetically identical). This has allowed the effects of experimental treatments on murine cancers to be evaluated in laboratory mice. Some inbred strains also spontaneously develop cancers (e.g. BALB/c mice frequently develop lung tumours), so the effects of cancer prevention strategies can be studied. The development of immunodeficient mice allowed the transfer and study of human cancer cells in mice without the mice rejecting the xenograft (graft between different species). The first immunodeficient mice were "nude mice", an inbred strain that lacks a thymus gland and T lymphocytes; they are hairless because of a mutation in a linked genetic locus. Subsequently, in 1983, even more immunodeficient severe combined immunodeficiency (SCID) mice were developed that lack both T and B cells. Genetically modified transgenic mice have been manufactured by knocking out specific genes ("knockout mice") or adding extra trans-genes, usually from different species ("transgenic mice"), to embryonic stem cells. These mice are used to elucidate the influence of individual genes on the phenotype. Finally,

mice were the original source of monoclonal antibodies produced by immunizing inbred mice with the desired antigen and fusing spleen cells from the mouse with myeloma cells to yield hybridoma cells that produce monoclonal antibodies.

Histopathological perspective

Cancer is usually defined by various histopathological features, most notably invasion and metastasis, that are observed by gross pathological and microscopic examinations. Laminin staining of the basement membrane may assist the histopathologist in identifying local invasion by tumours that breach the basement membrane. In addition, a number of microscopic features point to the diagnosis of cancer:

1. The arrangement of tumour cells (their "architecture") is less organized than that of their parent tissues, with heterogeneous cells of varying sizes and orientation with respect to one another despite their clonal origin (Figure 1.3).
2. Cancer cells have more nuclear DNA than normal cells, so they have comparatively larger nuclei, leading to a raised nuclear:cytoplasmic ratio (Figure 1.4).
3. Cancer cells may be multinucleated with several nuclei per cell or may have multiple prominent nucleoli (Figure 1.5).
4. Cancer cells divide frequently, so cancers have many mitotic figures (Figure 1.6).
5. Cancer cells will commonly have densely coloured or hyperchromatic nuclei with wrinkled nuclear edges (Figure 1.7).

Molecular perspective

At a molecular level, six basic steps or "hallmarks" that turn a cell into a cancer were described in 2000 by Douglas Hanahan and Robert Weinberg. In 2011,

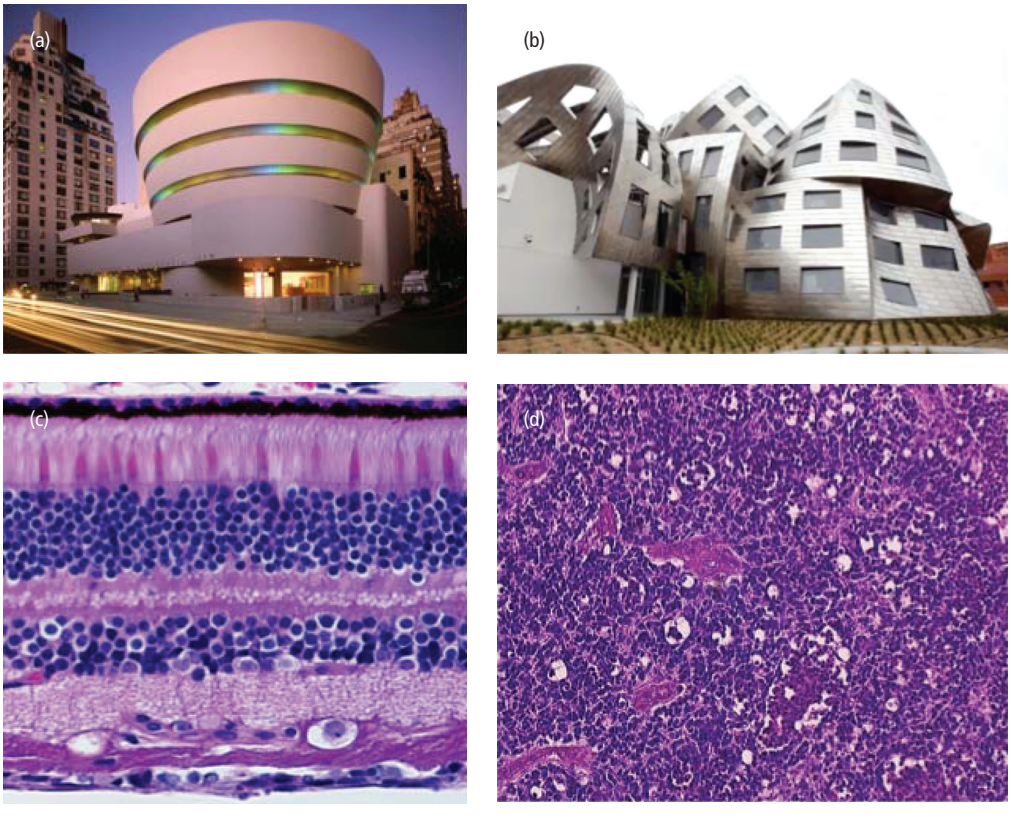


Figure 1.3 The Frank architecture of cancer. Normal tissue architecture is ordered, structured and controlled like a Frank Lloyd Wright building. Cancer tissues are higgledy-piggledy heaped on top of each other without any apparent planning like some of the buildings of Frank Gehry. (a) Frank Lloyd Wright designed the Guggenheim museum in New York. (b) Frank Gehry designed the Lou Ruvo centre for brain health in Las Vegas. (c) Normal retina histology. (d) Retinoblastoma histology.

High nuclear:cytoplasmic ratio

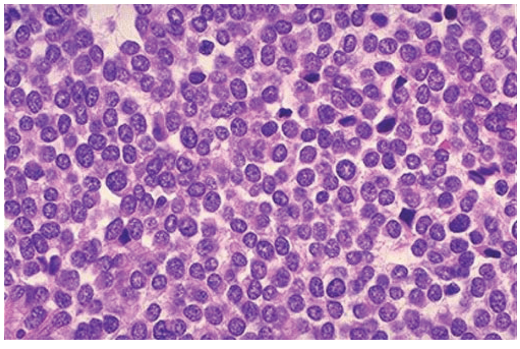


Figure 1.4 Ewing's sarcoma cells with large prominent purple nuclei surrounded by a thin pink rim of cytoplasm, demonstrating the high nuclear:cytoplasmic ratio of cancer cells.

a further two "enabling hallmarks" were added that contribute to the ability of cells to acquire the six hallmarks and a further two "emerging hallmarks" required for cancer cells to continue to survive as tumours. Molecular features that identify a cancer and make it behave differently from a normal cell are described in Chapter 2. The six original properties are:

1. Grow without a trigger (self-sufficiency in growth stimuli).
2. Do not stop growing (insensitivity to inhibitory stimuli).
3. Do not die (evasion of apoptosis).
4. Do not age (immortalization).
5. Feed themselves (neoangiogenesis).
6. Spread (invasion and metastasis).

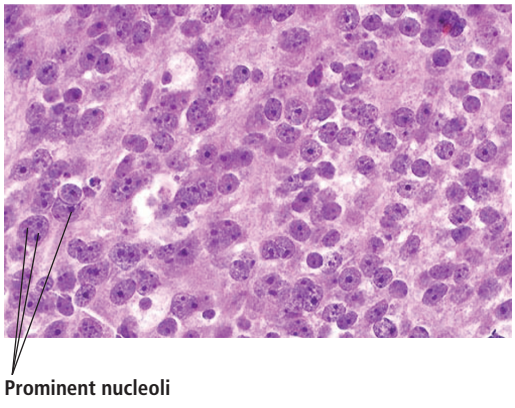


Figure 1.5 Many large dark nucleoi are seen here within the nuclei of cancer cells in this prostate adenocarcinoma.

Mitotic figure

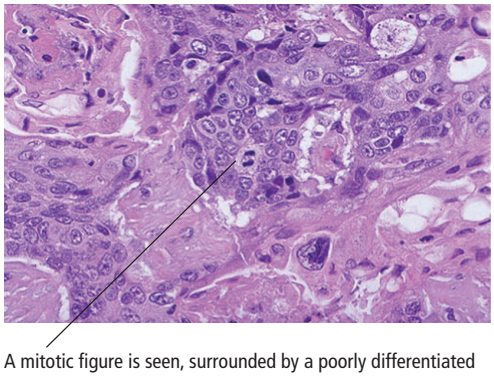


Figure 1.6 Poorly differentiated squamous cell lung cancer with a prominent mitotic figure.

How to read a histology report

The diagnosis of cancer is most commonly established following a histopathological examination of a biopsy or tumour resection (Figure 1.8). A histopathological report should include both gross pathological features (tumour size and number and size of lymph nodes examined) and microscopic findings (tumour grade, architecture, mitotic rate, margin involvement and lymphovascular invasion). The grade and stage of a cancer are important prognostic factors that may influence therapy options (Box 1.3).

Hyperchromatic nuclei

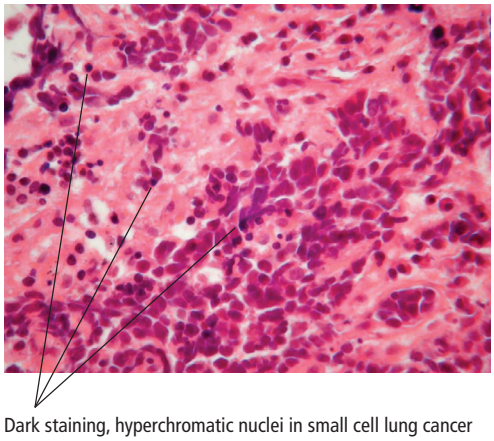


Figure 1.7 Small cell lung cancer containing several darkly stained hyperchromatic nuclei.

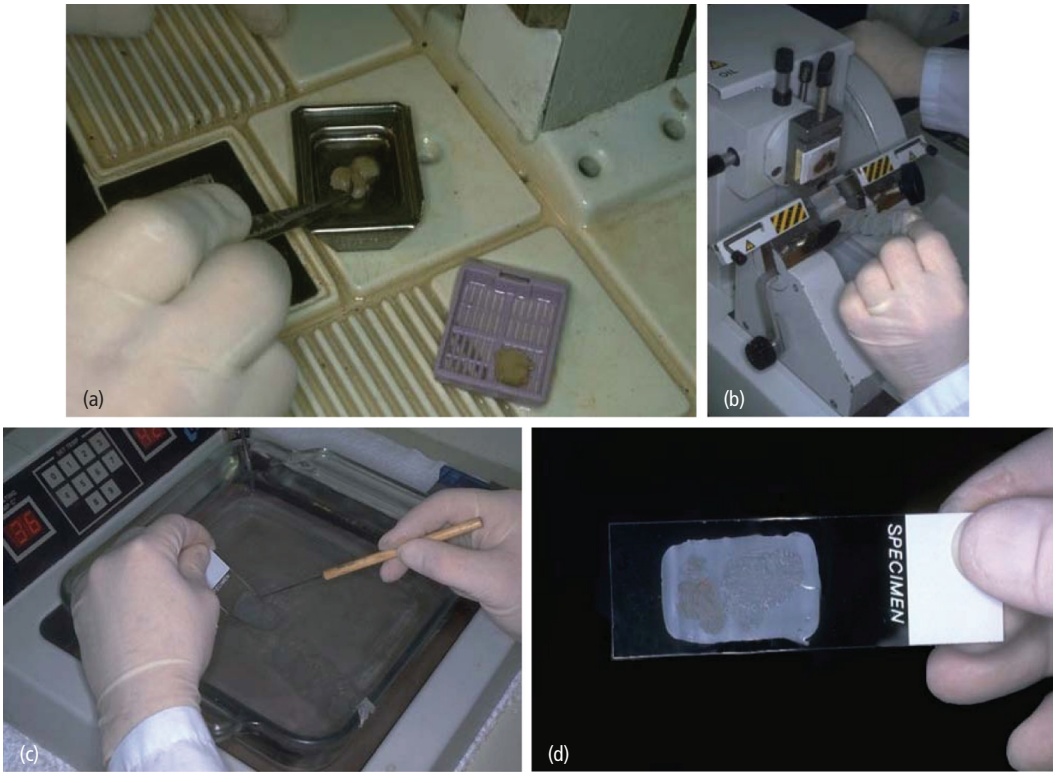


Figure 1.8 Preparing a histology slide. (a) Tissue is embedded in paraffin wax. (b) Thin sections of the tissue are sliced by a microtome. (c) Tissue sections are floated onto a glass slide. (d) The tissue sections on the glass slide are then stained.

Box 1.3 Histopathology definitions

Quantitative changes: too small

Atrophy

Acquired shrinkage due to a decrease in the *size or number* of cells of a tissue, for example, decrease in size of the ovaries after the menopause.

Quantitative changes: too big

Hypertrophy

Increase in the size of an organ or tissue due to an increase in the *size* of individual cells, for example, pregnant uterus.

Hyperplasia

Increase in the *size* of an organ due to an increase in the *number* of cells, for example, lactating breast.

Qualitative changes

Metaplasia

Replacement of one cell type in an organ by another. This implies changes in the differentiation programme and is usually a response to persistent injury. It is reversible so that removal of the source of injury results in reversion to the original cell

type; for example, squamous metaplasia of laryngeal respiratory epithelium in a smoker. Chronic irritation from smoking causes the normal columnar respiratory epithelium to be replaced by the more resilient squamous epithelium.

Dysplasia

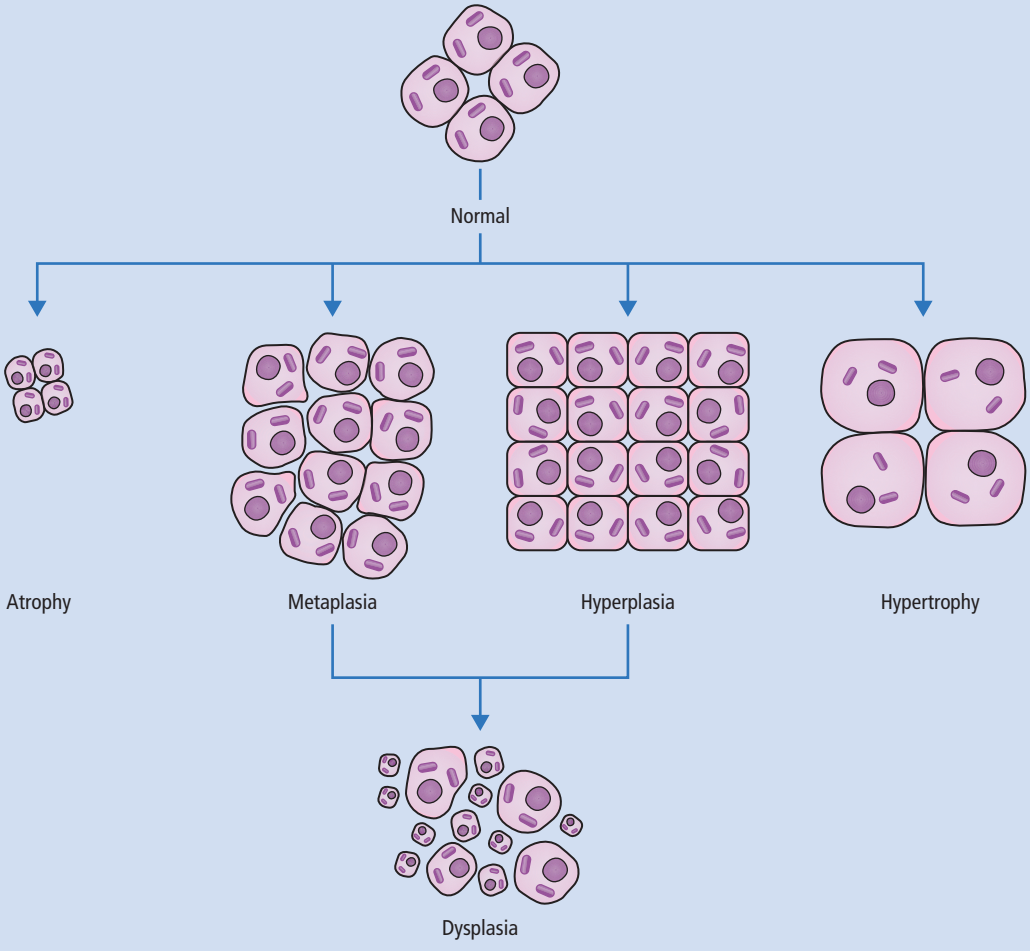
Dysplastic changes are changes in cell type, as for metaplasia, that do not revert to normal once the injury is removed; for example, cervical dysplasia initiated by human papillomavirus infection persists after eradication of the virus. Dysplasia is usually considered to be part of the spectrum of changes leading to neoplasia.

Invasion

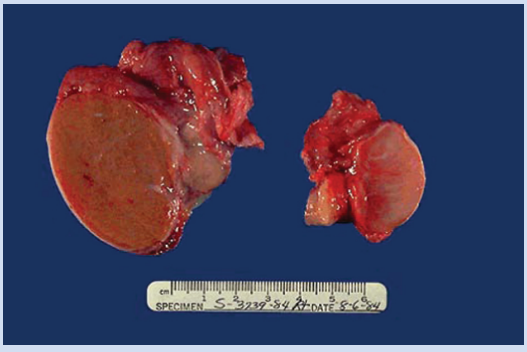
The capacity to infiltrate the surrounding tissues and organs is a characteristic of cancer.

Metastasis

The ability to proliferate in distant parts of the body after tumour cells have been transported by lymph or blood or along body spaces.

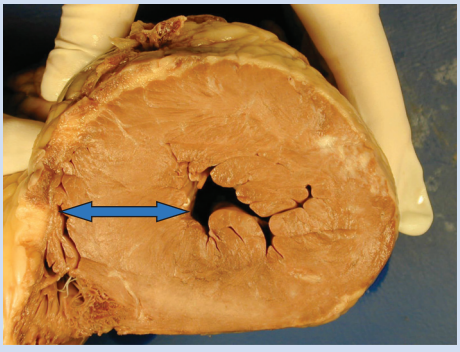


Atrophy of testes



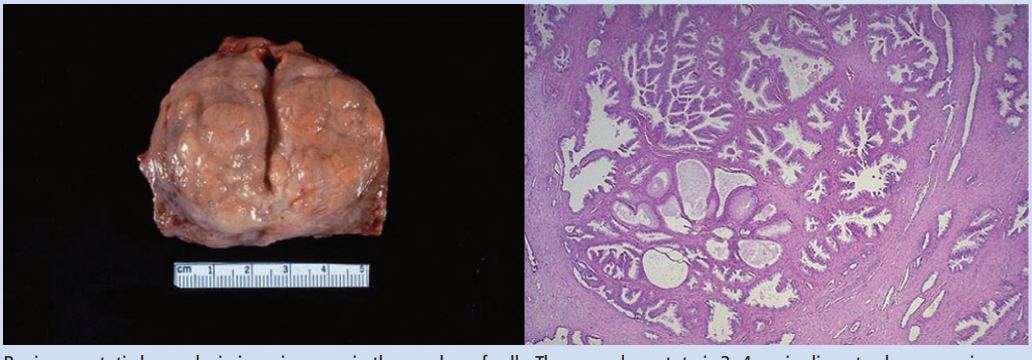
Testicular atrophy is a reduction in the size and function of the testes and may be caused by anabolic steroid use.

Hypertrophic cardiomyopathy (HCM)



Concentric thickening of the heart muscle caused by an increase in the size of the heart muscle cells (myocytes)

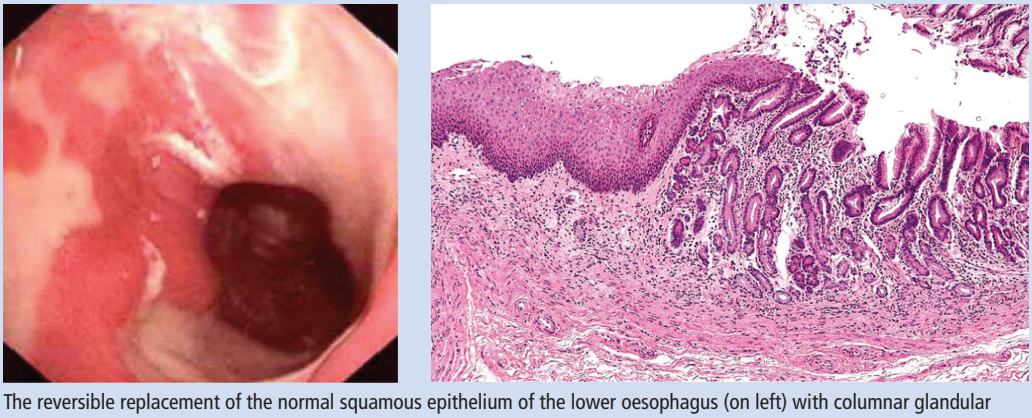
Hyperplasia of the prostate gland



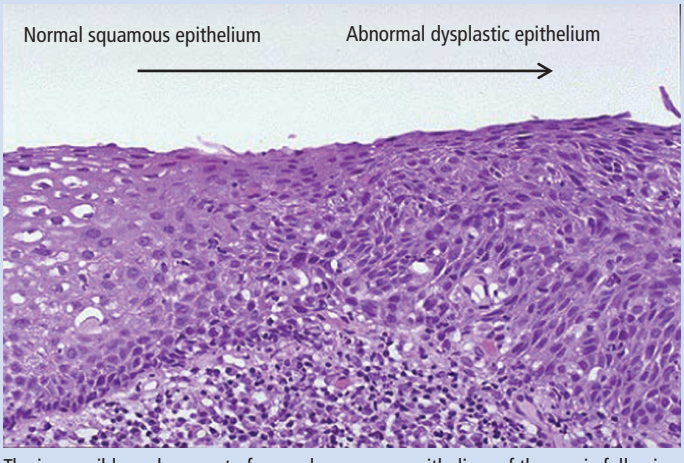
Benign prostatic hyperplasia is an increase in the number of cells. The normal prostate is 3–4 cm in diameter, by comparison. The prostate is filled with enlarged crowded glands, but there is still stroma between adjacent glands.

Metaplasia in Barrett's oesophagus

Normal squamous oesophageal mucosa → Columnar glandular epithelium



The reversible replacement of the normal squamous epithelium of the lower oesophagus (on left) with columnar glandular mucosa similar to that found in the stomach (on right)



The irreversible replacement of normal squamous epithelium of the cervix following human papillomavirus (HPV) infection. The normal squamous epithelium on the left transforms to a disorderly growth pattern on the right.

A histopathological definition of cancer: is it malignant or benign?

Malignancy is usually characterized by various behavioural features, most notably invasion and metastasis. However, the histopathologist may have to identify a cancer without this information. Cancers are composed of clonal cells (all are the progeny of a single cell) and have lost control of their tissue organization and architecture. In addition to the natural history, a number of physical properties help to distinguish between benign and malignant tumours (Table 1.3). However, there is no single histological feature that defines a cancer nor indeed that separates benign from malignant tumours. In general, benign tumours are rarely life-threatening but may cause health problems on account of their location (by pressure or obstruction of adjacent organs) or by overproduction of hormones. In contrast, malignant tumours usually follow a progressive course and unless successfully treated are frequently fatal.

Table 1.3 Histological features of benign and malignant tumours

Features of malignancy	Features of benign tumours
Macroscopic features	
Invade and metastasize	Do not invade or metastasize
Rapid growth	Slow growing
Not clearly demarcated	Clearly demarcated from surrounding tissue
Surface often ulcerated and necrotic	Surface smooth
Cut surface heterogenous	Cut surface homogenous
Microscopic features	
Often high mitotic rate	Low mitotic rate
Nuclei pleomorphic and hyperchromatic	Nuclear morphology often normal
Abnormal mitoses	Mitotic figures normal

Is it *in situ* or invasive?

Invasive cancers extend into the surrounding stroma (Figure 1.9). However, tumours that exhibit all the microscopic features of cancers but do not breach the original basement membrane are termed *in situ* (non-invasive) cancers. Examples include *in situ* breast cancer confined to the mammary ducts (ductal carcinoma *in situ* (DCIS)) or lobules (lobular carcinoma *in situ* (LCIS)) (Figure 1.9). Similar pre-invasive *in situ* cancers have been found in many organs (e.g. cervix, anus, prostate, bronchus) and are believed to represent a stage in the progression from dysplasia to cancer (Figure 1.10).

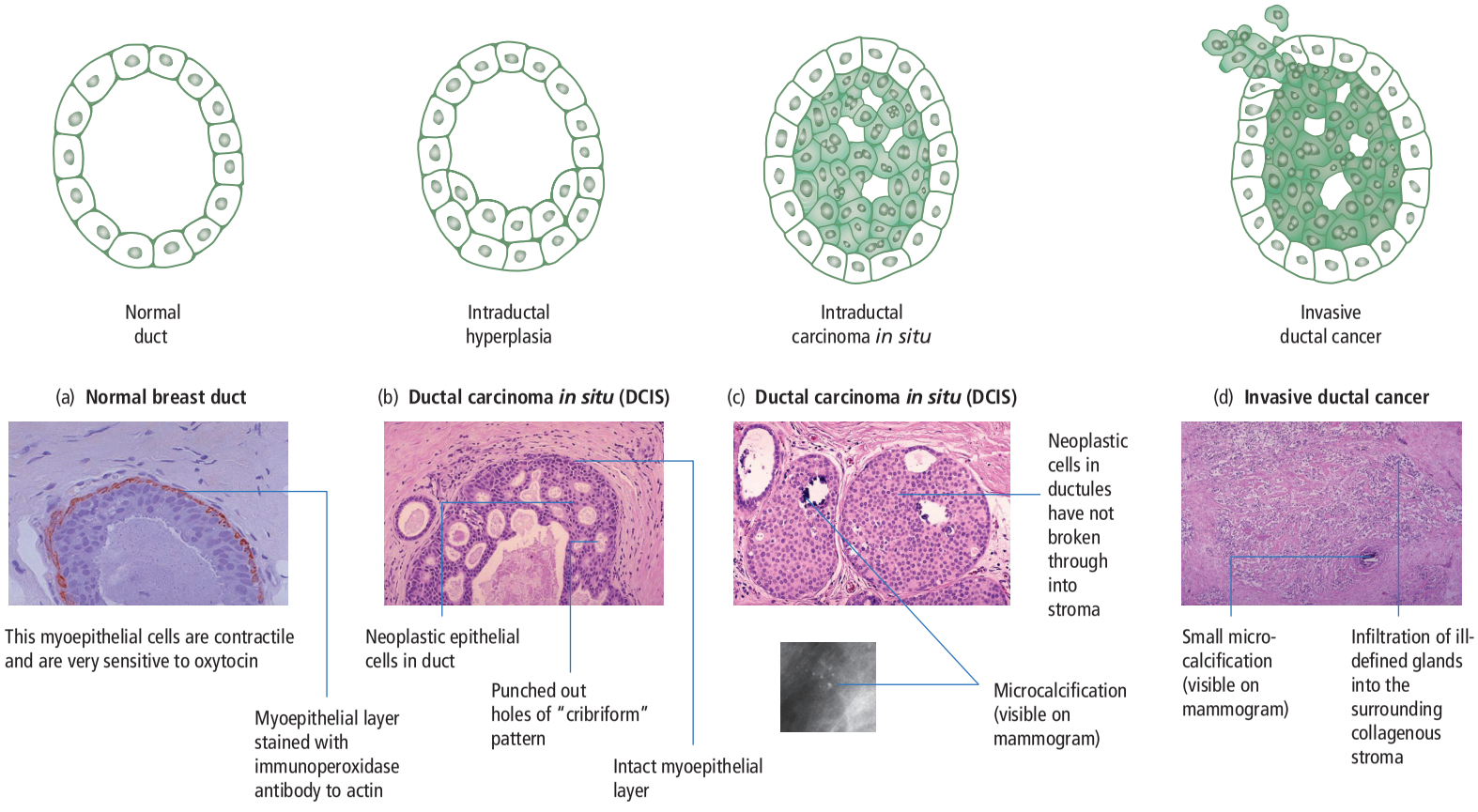


Figure 1.9 (a) Normal breast duct. (b)+(c) Ductal carcinoma *in situ* (DCIS). (d) Invasive ductal cancer.

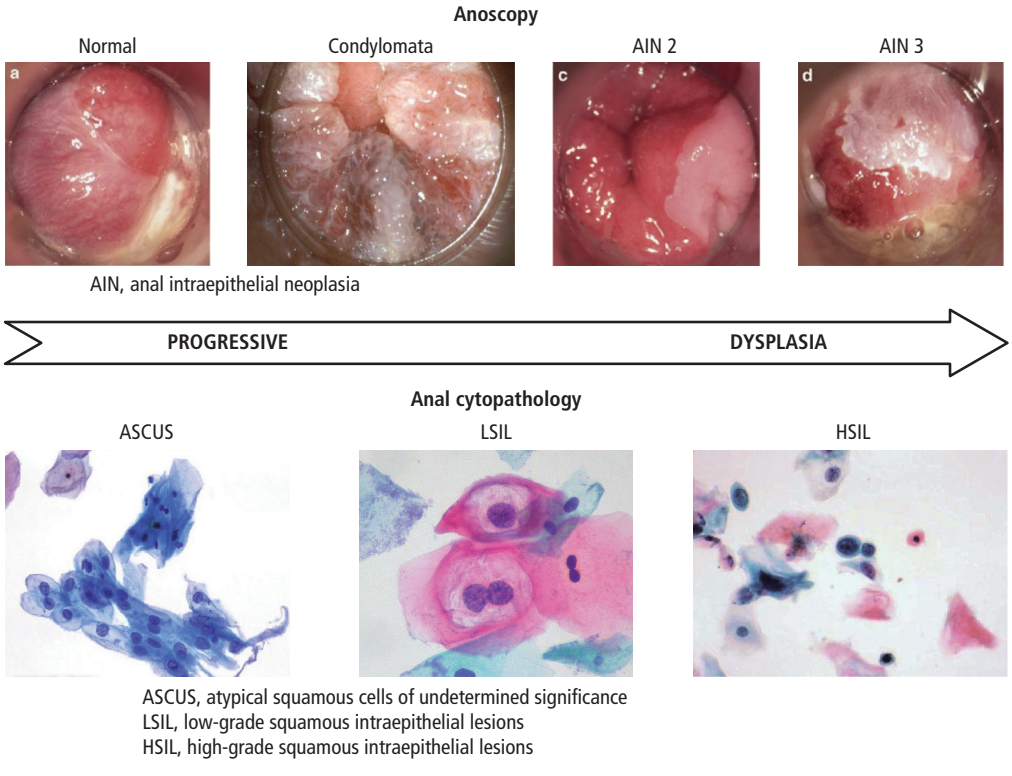


Figure 1.10 Progression of pre-invasive anal cancer with associated cytopathology changes.

Histopathologist's nomenclature: name that cancer

The histopathologists' lexicon often can be a tool for obfuscation, but follow a few simple rules and you can translate their lingo. The suffix -oma usually denotes a benign tumour (although it simply means "swelling" and some -omas are not tumours, e.g. xanthoma). If a tumour is malignant, the suffix -carcinoma (Greek for crab) is used for epithelial cancers or -sarcoma (Greek for flesh) for connective tissue cancers. The prefix is determined by the cells of origin of the tumour (e.g. adeno- for glandular epithelium), qualified by the tissue of origin (e.g. prostatic adenocarcinoma). There are numerous exceptions to this systematic nomenclature; for example, leukaemias and lymphomas are malignant tumours of the bone marrow and lymphoid tissue, respectively. As a general rule, neoplasms are classified according to the type of normal tissue they most closely resemble. The four major categories are: epithelial, connective tissue, lymphoid and haemopoietic tissue, and germ cells (Tables 1.4, 1.5, 1.6 and 1.7). The latter arises in totipotential cells and can develop into any cell type. Germ cell tumours

Table 1.4 Nomenclature of epithelial tumours

Epithelium	Benign tumour	Malignant tumour
Squamous	Squamous papilloma	Squamous carcinoma
Glandular	Adenoma	Adenocarcinoma
Transitional	Transitional papilloma	Transitional carcinoma
Liver	Hepatic adenoma	Hepatocellular carcinoma
Skin	Papilloma	Squamous cell carcinoma Basal cell carcinoma
Skin melanocyte	Naevus	Malignant melanoma

Table 1.5 Nomenclature of connective tissue tumours

Tissue	Benign tumour	Malignant tumour
Bone	Osteoma	Osteosarcoma
Cartilage	Chondroma	Chondrosarcoma
Fat	Lipoma	Liposarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Blood vessel	Angioma	Angiosarcoma
Fibrous tissue	Fibroma	Fibrosarcoma

Table 1.6 Nomenclature of haematological tumours

Tissue	Malignant tumour
Node lymphocyte	Lymphoma
Marrow lymphocyte	Lymphocytic leukaemia
Granulocyte	Myeloid leukaemia
Plasma cell	Myeloma

contain a variety of different mature and/or immature tissues from different embryonic germ layers and these are given names with the root terato- (Greek for monster). In addition, as with most fields of medicine where physicians try to leave their mark, there are a number of eponymous names (e.g. Hodgkin's disease). In 1832, Thomas Hodgkin (of Guy's Hospital) described seven cases of the tumour that bears his name, but re-examination in 1926 revealed that the diagnosis was inaccurate in four of the seven cases.

Tumour grading

Tumours are graded according to the degree of tissue differentiation (Box 1.4). Cancers that closely resemble their tissue of origin are graded as well-differentiated cancers. Cancers that look nothing like the original tissue and have histological features of aggressive growth with high mitotic rates are graded as poorly differentiated cancers. The grade of a tumour is of prognostic significance (Figure 1.11).

In addition, pathologists may identify other features that relate to the natural behaviour of a tumour, such as lymphovascular invasion and perineural invasion, which usually denotes a worse prognosis (Figure 1.14). The molecular properties of a cancer can also influence the biology, prognosis and treatment of a tumour. For example, the gene expression prolife of a breast cancer may be determined by gene expression microarray chip technology, and the results assist clinicians in optimizing adjuvant therapy (Figure 1.12).

Unknown primary identification (standard histological techniques)

Occasionally patients present with metastatic cancer without an obvious primary tumour site and, in addition to a careful clinical and radiological examination, the pathologist may provide a clue to the origins of the cancer. Most unknown primary cancers are adenocarcinoma (60%) and the remainder are poorly differentiated carcinomas (30%) and squamous cell carcinomas (5%). Light microscopy may provide pointers; for example, the presence of melanin pigment favours melanoma, whilst the presence of mucins, which are gel-forming lubricating proteins, is common in gastrointestinal, breast and lung cancers but less

Table 1.7 Nomenclature of germ cell tumours

Tissue	Benign tumour	Malignant tumour (male)	Malignant tumour (female)
Germ cell	Mature teratoma/ dermoid cyst	Non-seminomatous germ cell tumour/ malignant teratoma	Immature teratoma/embryonal carcinoma
	–	Seminoma	Dysgerminoma

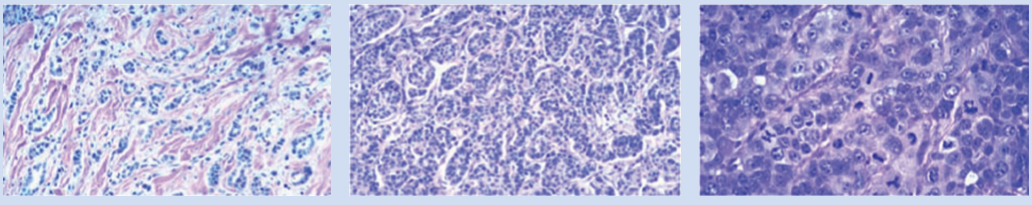
Box 1.4 Grading breast cancer (Scarff–Bloom–Richardson system)

1 Frequency of cell mitosis (score 1–3)

2 Tubule formation (score 1–3)

3 Nuclear pleomorphism (score 1–3)

Total score: 3–5 = Grade 1 tumour (well differentiated), 6–7 = Grade 2 (moderately differentiated), 8–9 = Grade 3 (poorly differentiated). The 5-year overall survival for grades 1, 2 and 3 are 95%, 75% and 50%, respectively.



Grade 1
Well differentiated (bad)

Grade 2
Moderately differentiated (worse)

Grade 3
Poorly differentiated (worst)

Figure 1.11 Grading breast cancer.

common in ovarian cancers and is rare in renal and thyroid cancers. Immunocytochemical staining of tissue samples uses antibodies to specific proteins to aid the pathologist in tissue identification. For example, the presence of oestrogen and progesterone receptors favours a diagnosis of breast cancer (Figure 1.13), whilst prostate-specific antigen and prostatic acid phosphatase staining points to prostatic adenocarcinoma. Similarly, cytokeratin expression patterns may provide helpful hints about the origin of metastatic cancers (Box 1.5). Cell surface immunophenotyping is a sophistication of immunocytochemistry that is frequently applied to haematological malignancies. The pattern of immunoglobulin, T-cell receptor and cluster designation (CD) antigen expression on the surface of lymphomas is helpful in their diagnosis and classification. Immunophenotyping can be achieved by immunohistochemical staining, immunofluorescent staining or flow cytometry.

Unknown primary identification (special histological techniques)

The study of intracellular organelles by electron microscopy may identify the cellular origin of a tumour; for example, the presence of melanosomes in melanomas and dense core neurosecretory granules in neuroendocrine tumours. Further laboratory techniques to aid diagnosis include molecular studies of DNA rearrangements that characterize malignancies. Monoclonal immunoglobulin gene rearrangements are present in B-cell malignancies and rearrangements of T-cell receptor genes occur in T-cell tumours. In addition, a number of chromosomal translocations involving the immunoglobulin genes (heavy chain on chromosome 14q32, light chains on 2p12 and 22q11) and T-cell receptor genes (TCRα on 14q11, TCRβ on 7q35, TCRγ on 7p15, TCRδ on 14q11) occur in malignancies arising from these cell types. For instance, low-grade follicular lymphomas rearrange the Bcl-2 gene on 18q21 (e.g. t(14;18)(q32;q21)), most Burkitt lymphomas rearrange the Myc oncogene on 8q24 (e.g. t(8;14)(q24;q32)) and most mantle cell lymphomas rearrange Bcl-1 on 11q13 (e.g. t(11;14)(q13;q32)). These rearrangements may be detected by karyotype analysis of mitotic chromosome preparations or by molecular techniques including Southern blotting and polymerase chain reaction (Box 1.6 and Table 1.8). Less commonly, these same methods may assist the diagnosis of solid tumours that are associated with specific chromosomal abnormalities such as the i(12p) isochromosome found in germ cell tumours and the t(11;22)(q24;q12) translocation seen in Ewing's sarcoma and peripheral neuroectodermal tumours. In addition to translocations, gene amplification may be detected and may have prognostic significance; for example, the amplification of the n-Myc oncogene in neuroblastoma is an adverse prognostic variable.

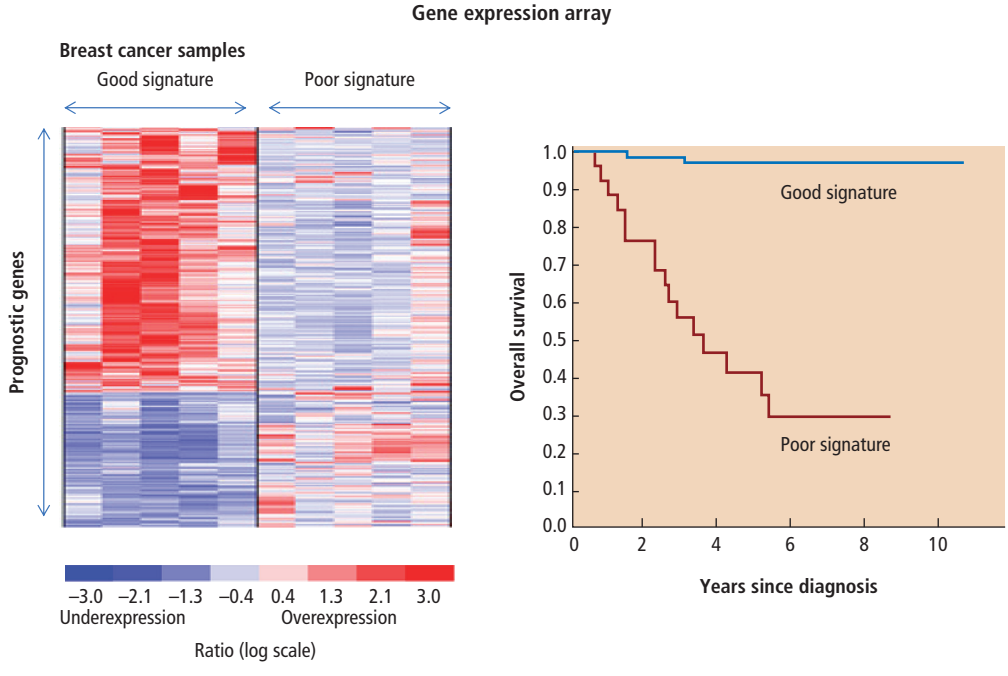
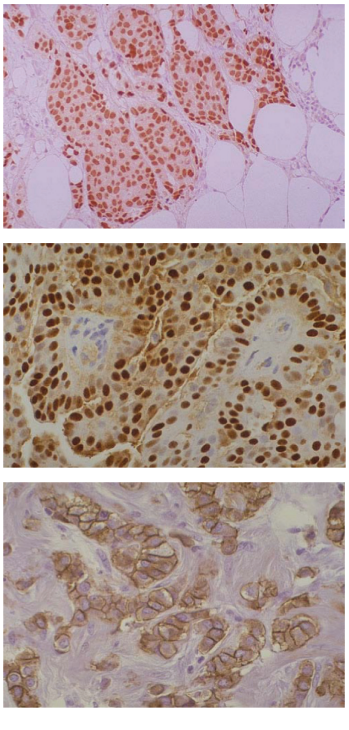


Figure 1.12 Gene expression profiles for breast cancer samples differentiate tumours into good- and poor-prognosis signatures that predict survival.



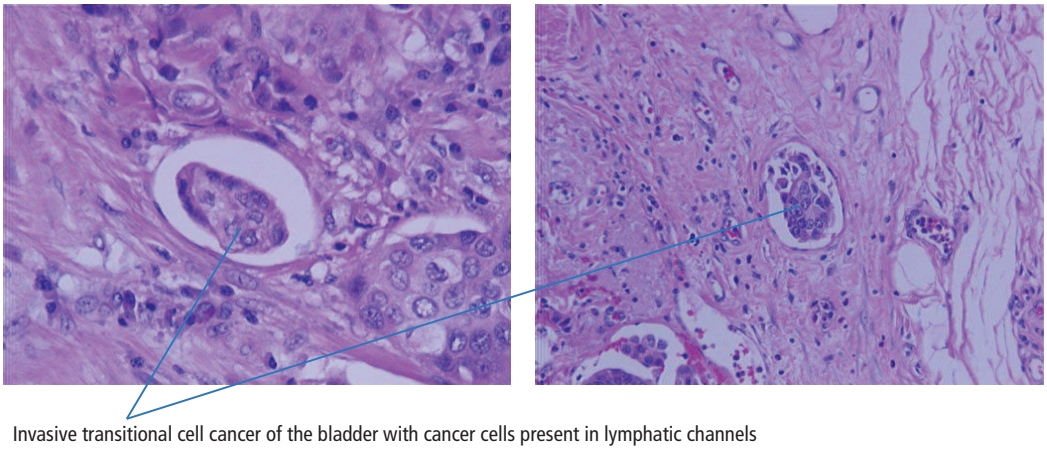
ER (oestrogen receptor) expression

PR (progesterone receptor) expression

C-erbB-2 (HER2-neu) expression

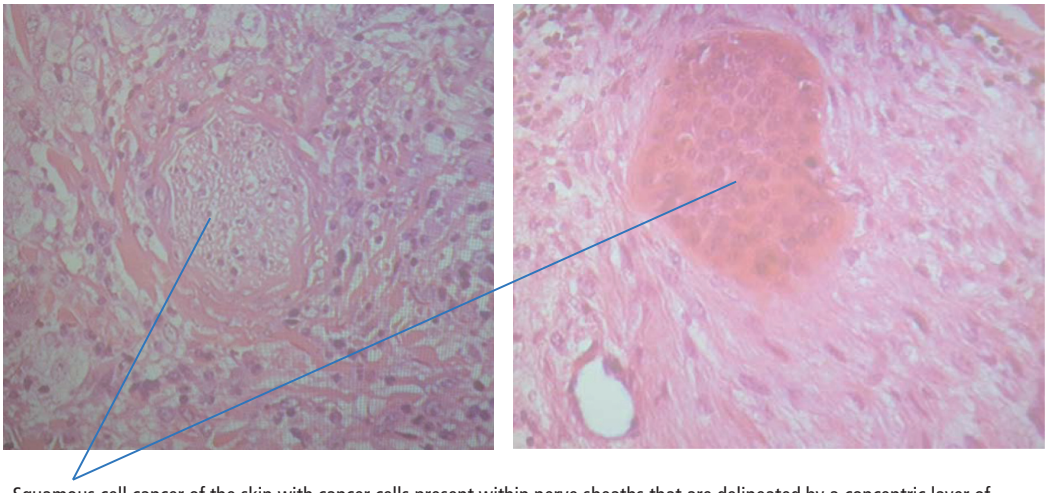
Membranous staining for c-erbB2 (HER2-neu) correlates with high grade and poor differentiation. C-erbB2 (human epidermal growth factor 2) is the target of the monoclonal antibody therapy Herceptin (trastuzumab)

Figure 1.13 Immunocytochemical staining in breast cancer.



Invasive transitional cell cancer of the bladder with cancer cells present in lymphatic channels

(a)



Squamous cell cancer of the skin with cancer cells present within nerve sheaths that are delineated by a concentric layer of perineural epithelial cells

(b)

Figure 1.14 (a) Lymphatic invasion and (b) perineural invasion.

Cancer epidemiology

Epidemiology in the United Kingdom

Cancer is now the most common cause of death in the United Kingdom (if cardiovascular and cerebrovascular diseases are classed separately).

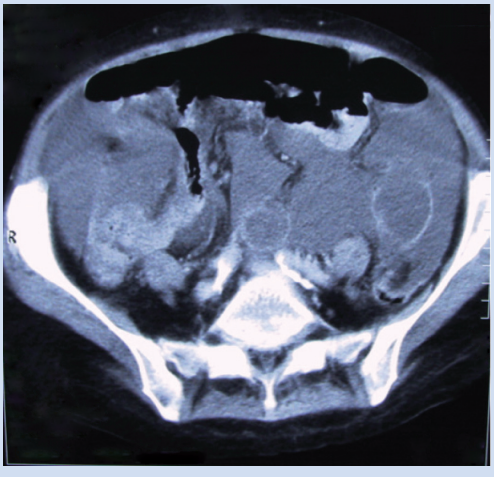
- One in three people in the United Kingdom will develop a cancer (434,115 in 2011).
- One in four die of cancer (159,178 in 2011).

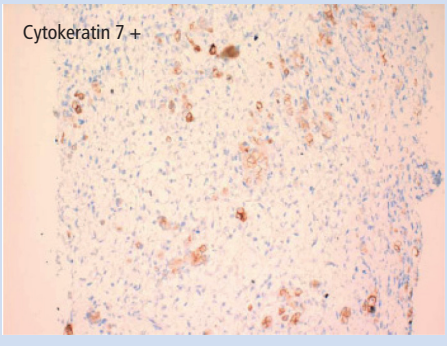
Global epidemiology

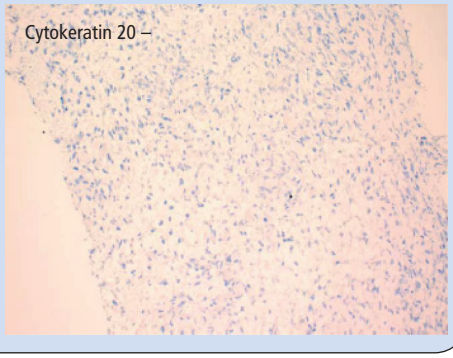
The current world population is 6 billion with 10 million new cancer cases and 6 million cancer deaths annually. Projections for 2020 are a global population of 8 billion; 20 million new cancer cases and 12 million deaths annually. Tobacco contributes to 3 million cases (chiefly lung, head, neck and bladder cancers), diet to an estimated 3 million cases (upper gastrointestinal, colorectal) and infection to a further 1.5 million cases (cervical, stomach, liver, bladder and lymphomas) globally. The incidence of different types of cancer varies geographically

Box 1.5 Cytokeratins

Cytokeratins are intermediate filament proteins that form the cytoskeleton within a cell. They are expressed in pairs comprising a type I (cytokeratins 9–20) and a type II (cytokeratins 1–8) cytokeratin. Different tissues express different pairs and immunocytochemical staining for cytokeratins can help identify the likely tissue origins of cancers cells. For example, in disseminated peritoneal metastases, CK7 expression favours an ovarian origin, whilst lack of CK7 is more common in colorectal cancer (Figure 1.3).







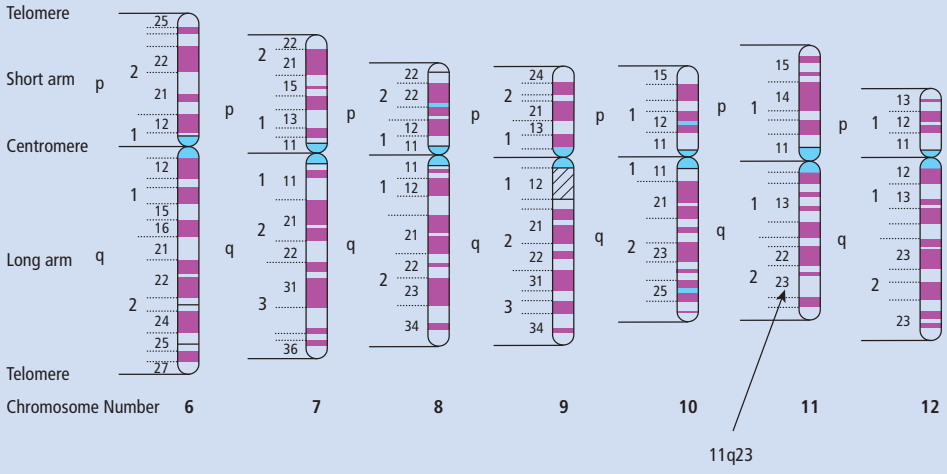
A 78-year-old woman presents with bowel obstruction and ascites. The CT scan shows extensive ascites and omental thickening. CT-guided biopsy of peritoneal deposits demonstrates adenocarcinoma, immunocytochemistry for cytokeratins (CK7+ and CK20–) suggests an ovarian rather than colonic primary

according to the risk factors and demographics of the local population (Figure 1.15) However, there is a general correlation between increasing wealth and increasing cancer incidence. This is attributable to tobacco use, diet and increased longevity in wealthy populations. There are intriguing exceptions; for example, the Gulf States of Kuwait, Qatar, Bahrain, United Arab Emirates and Saudi Arabia have lower cancer incidences than would be predicted from their per capita gross national product. Consideration also has to be given to the variable standard of reporting of cancer statistics in different countries.

Table 1.8 Examples of chromosomal abnormalities in cancers

Chromosome defect	Karyotype	Tumour	Candidate gene
Monosomy	45,XY –22	Meningioma	NF2
Trisomy	47,XX +7	Papillary renal carcinoma	MET
Deletion	46,XY del(11)(p13)	Wilms' tumour	WT1
Duplication	46,XX dup(2)(p23-24)	Neuroblastoma	n-Myc
Inversion	46,XY inv(16)(p13q22)	Acute myeloid leukaemia (M4Eo)	MYH11/core-binding factor b
Isochromosome	47,XX i(12p)	Testicular germ cell tumour	
Translocation	46,XX t(9;22)(q34;q11)	Chronic myeloid leukaemia	bcr/abl

Box 1.6 The language of chromosomes – karyotype nomenclature



Each arm of a chromosome is divided into one to four major regions, depending on the chromosomal length; each band, positively or negatively stained, is given a number that rises as the distance from the centromere increases. The normal male is designated as 46,XY and the normal female as 46,XX.

For example, 11q23 designates the chromosome (11), the long arm (q), the second region distal to the centromere (2) and the third band (3) in that region.

Polyploid

A cell with more than one complete chromosome set or with multiples of the basic number of chromosomes characteristic of the species; in humans this would be 69,92, etc.

Aneuploid

Individual with one or more chromosomes in addition or missing from the complete chromosome set; for example, trisomy 21 (47,XX +21).

Deletion

The loss of a chromosome segment from a normal chromosome.

Duplication

An extra piece of chromosome segment which may be attached to the same homologous chromosome or transposed to another chromosome in the genome.

Inversion

A change in the linear sequence of the genes in a chromosome that results in the reverse order of genes in a chromosome segment. Inversions may be pericentric (two breaks on either side of the centromere) or paracentric (both breaks on the same arm).

Isochromosome

Breaks in one arm of a chromosome followed by duplication of the other arm of the chromosome to produce a chromosome with two arms that are both short (p) or both long (q) arms.

Translocations

Translocations are the result of the reciprocal exchange of terminal segments of non-homologous chromosomes.

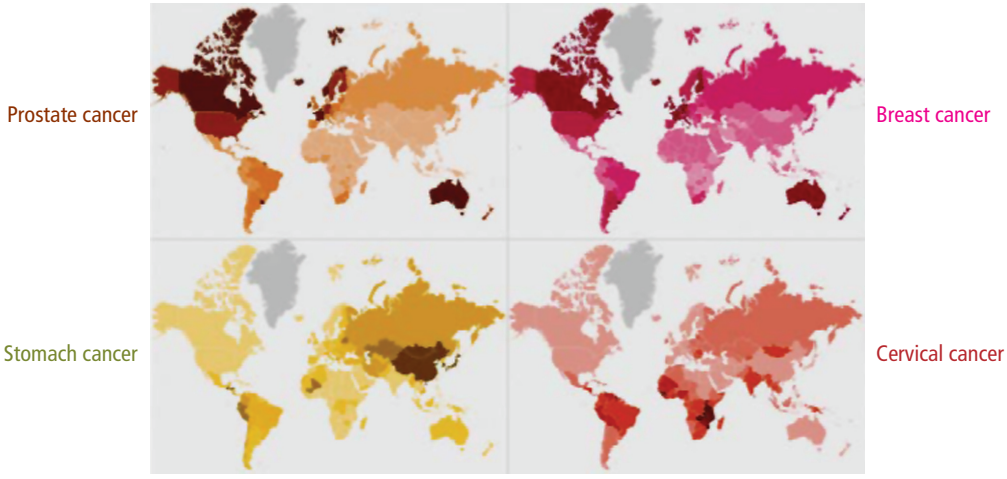


Figure 1.15 Global incidences for prostate, breast, stomach and cervical cancers. Darker colours denote higher incidence.

Cancer charities

Cancer charities

The United Kingdom has 640 cancer charities to counter the disease. Their expenditure increases awareness of cancer, improves diagnosis and treatment capability and provides care for patients with the disease. The total income generated by the top 20 UK cancer charities in 2004 was £758 million, and the average charitable efficiency was 64% providing £488 million for spending on patients' care and research. The two largest UK cancer charities, the Imperial Cancer Research Fund (ICRF) and the Cancer Research Campaign (CRC) merged to form Cancer Research UK (CRUK) in 2002. CRUK is the largest volunteer-supported cancer research organization in the world, with 3000 scientists and an annual scientific spend of more than £460 million – raised almost entirely through public donations.

Cancer hospitals

Philanthropists and social reformers during the 19th century tried to provide free medical care for the poor. William Marsden, a young surgeon opened a dispensary for advice and medicines in 1828. His grandly named London General Institution for the Gratuitous Cure of Malignant Diseases – a simple four-storey house in one of the poorest parts of the city – was conceived as a hospital to which the only passport should be poverty and disease and where treatment was provided free of charge. The demand for Marsden's free services was overwhelming, and by 1844 his dispensary, now called the Royal Free Hospital, was treating 30,000 patients a year. In 1846 when his wife died of cancer, Marsden opened a small house in Cannon Row, Westminster, for patients suffering from cancer. Within 10 years, the institution moved to Fulham Road and became known as the Cancer Hospital, of which Marsden was the senior surgeon. The hospital was incorporated into the National Health Service in 1948 and renamed the Royal Marsden Hospital in 1954. Although other cancer hospitals have been established in Manchester (the Christie Hospital) and Glasgow (the Beatson Hospital), the Royal Marsden Hospital remains the most renown. With the recent emphasis on multidisciplinary approaches to cancer, single specialty hospitals are less in vogue and the majority of cancer departments are within large teaching hospitals.

Cancer celebrities

Celebrities influence public perceptions and behaviour inordinately and this is as true in oncology as elsewhere. Celebrities with cancer have contributed in three main ways: personal accounts bring patients' experiences into the limelight, reports of celebrity patients increase public awareness and may encourage health-seeking behaviour such as stopping smoking and celebrity patients may support cancer charities and encourage donations. Prominent examples of