# Human cancers by organ site

Malignant tumours can develop in any organ from cell types still actively engaged in replication. The nomenclature refers to the tissue of origin: carcinoma (derived from epithelial tissues), sarcoma (soft tissues and bone), glioma (brain), leukaemia and lymphoma (haematopoietic and lymphatic tissues), carcinomas being by far the most frequent type. Irrespective of the site, malignant transformation is a multi-step process involving the sequential accumulation of genetic alterations. However, the types of oncogene or suppressor genes involved and the sequence of amplification or mutation varies greatly in different organs and target cells. Susceptibility to carcinogenic factors may depend on the capacity to metabolize chemical carcinogens, to effectively repair DNA damage or to harbour chronic infections. There are also marked variations in response to therapy and overall clinical outcome.
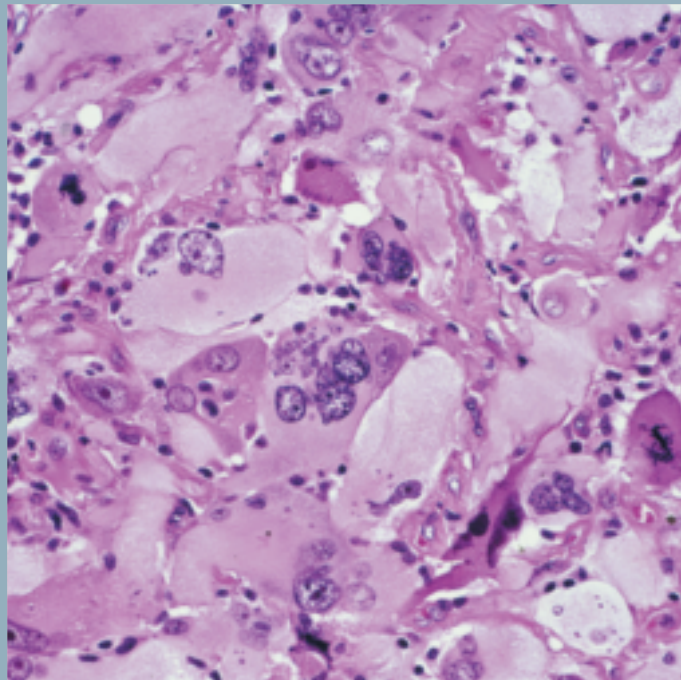
LUNG CANCER

SUMMARY

> Lung cancer is the most common tumour worldwide, with 900,000 new cases each year in men and 330,000 in women It is the leading cause of death from cancer.

> In men, more than 80% of lung cancer cases are caused by smoking; in women, the attributable risk is less (about 70% in Northern Europe; 45% worldwide).

> Some occupational exposures and air pollution (including environmental tobacco smoke) make a minor contribution to incidence.

> No population-based screening procedures have been established.

> No effective treatment is available; the five-year survival rate for lung cancer patients is less than 15%.

<5.7   <16.7   < 27.8   < 48.4   < 95.5
Age-standardized incidence/100,000 population

Fig. 5.1 The global incidence of lung cancer in men. Incidence is highest in Europe, especially Eastern Europe, and in North America and Australia.

Definition

Lung cancer almost exclusively involves carcinomas, these tumours arising from epithelia of the trachea, bronchi or lungs. There are several histological types, the most common being squamous cell carcinoma, adenocarcinoma and small (oat) cell carcinoma.

Epidemiology

Lung cancer is the most common malignant disease worldwide, and is the major cause of death from cancer, particularly amongst men. It was a rare disease until the beginning of the 20th century. Since then, the occurrence of lung cancer has increased rapidly and it now accounts for an estimated 901,746 new cases each year among men and 337,115 among women [1].
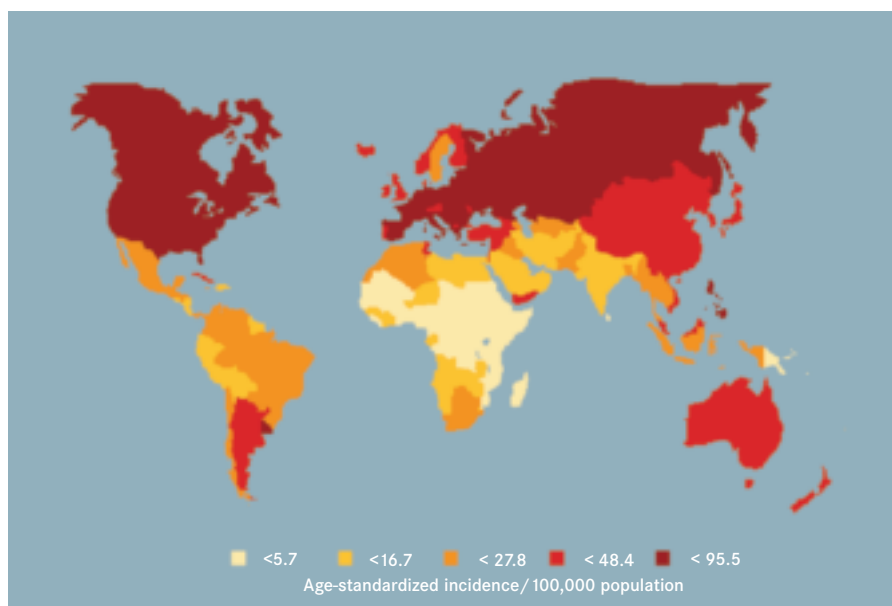The highest incidence rates (>100 cases per 100,000 population) are recorded among Afro-Americans from New Orleans, USA and Maoris from New Zealand and are followed by those in the United Kingdom and the Netherlands. The lowest incidence rates are reported from Africa and Southern Asia [2] (Fig. 5.1). Rates in women are high in the USA, Canada, Denmark and the UK, but are lower in countries such as France, Japan and Spain, in which the prevalence of smoking in women has increased only recently. The lowest rates (<3 cases per 100,000 population) are recorded in Africa and India. In most countries, lung cancer incidence is greater in lower socioeconomic classes; to a large extent, this pattern is explained by differences in the prevalence of smoking. Having risen dramatically since the turn of the century, lung cancer mortality amongst males is now abating in several countries, including the USA, the UK and Finland (Fig. 5.4).

Etiology

The geographical and temporal patterns of lung cancer incidence are overwhelmingly determined by consumption of tobacco. The association between lung cancer and smoking is probably the most intensively investigated relationship in epidemiology. Smoking causes lung cancer. An increase in tobacco consumption is paralleled some 20 years later by an increase in the incidence of lung cancer, and a decrease in consumption (e.g. a large proportion of smokers who quit) is followed by a decrease in incidence. In both men and women, the incidence of lung cancer is low before age 40, and increases up to at least age 70. The situation in China appears to be different, given the relatively high rates of lung cancer (particularly adenocarcinoma) recorded among Chinese women, despite a low prevalence of smoking.
The association between lung cancer and smoking was demonstrated in the 1950s and has been recognized by public health and regulatory authorities since the mid-1960s. The risk of lung cancer among smokers relative to the risk among never-smokers is in the order of 8-15 in men and 2-10 in women. This overall risk reflects the contribution of the different aspects of

tobacco smoking: age at start, average consumption, duration of smoking, time since quitting, type of tobacco product and inhalation pattern, with duration being the dominant factor. While lung cancer risks rise sharply with increasing numbers of cigarettes per day, the trends have been reported to be even stronger with duration of smoking. Such findings are essentially consistent in men from diverse communities, including those of the USA, UK and China. In populations with a long duration and heavy intensity of cigarette usage, the proportion of lung cancer attributable to smoking is of the order of 90% [3].

As compared to continuous smokers, the excess risk sharply decreases in ex-smokers approximately five years after quitting, but a small excess risk persists in long-term quitters throughout life. The risk of lung cancer is slightly lower among smokers of low-tar and low-nicotine cigarettes than among other smokers, although "low-tar smokers" tend to compensate for lower yields of nicotine by deeper inhalation or greater consumption. A relative reduction in risk has also been observed among long-term smokers of filtered cigarettes compared to smokers of unfiltered cigarettes. Smokers of black (air-cured) tobacco cigarettes are at a two to three-fold higher risk of lung cancer than smokers of blond (flue-cured) tobacco cigarettes. A causal association with lung cancer has also been shown for consumption of cigars, cigarillos, pipe, bidis and water pipe.

An association between exposure to passive smoke and lung cancer risk in non-smokers has been shown in a number of case-control and cohort studies (Fig. 5.9). In general, such studies involve exposure to environmental tobacco smoke in the home or the workplace or both. In many instances, the increased risk recorded is at the margin of statistical significance, and in some cases less than that. However, a causal relationship has been recognized on the basis of consistent findings and taking account of biological plausibility (that is, the established carcinogenic activity of tobacco smoke). The magnitude of the risk is in the order of 15-20% [4].

Occupational exposures have been associated with increased risk of lung cancer more than of any other tumour type (*Occupational exposures*, p33). For many workplace exposures associated with a high risk of lung cancer, the specific agent(s) responsible for the increased risk has been identified. Risk of lung cancer and mesothelioma (a malignant tumour of the pleura) is increased in a variety of occupations involving exposure to asbestos of various types. A characteristic of asbestos-related lung cancer is its synergistic relationship to cigarette smoking: risk is increased multiplicatively amongst persons who both smoke and are exposed to asbestos. Such a phenomenon has been recorded in relation to other occupational lung cancers.

Atomic bomb survivors and patients treated with radiotherapy are at increased risk

Fig. 5.2 The incidence of smoking-induced lung cancer in women is increasing in many countries at an alarming rate.

Fig. 5.3 Smoking is the primary cause of lung cancer. "Every cigarette is doing you damage" campaign, Australia.
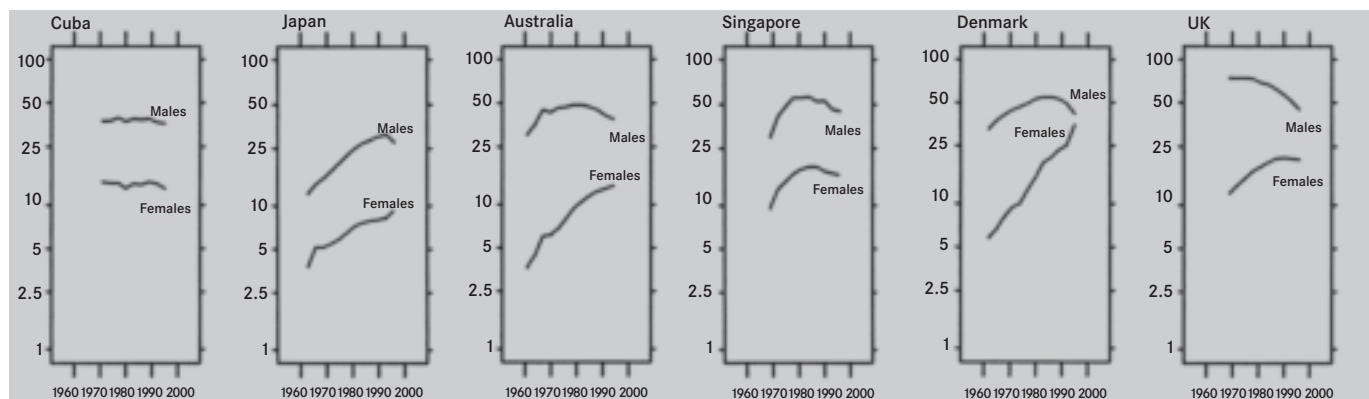

Fig. 5.4 Trends in mortality from lung cancer in men and women. Countries in which the smoking habit was first established are also the first to show decreases in mortality following reduction in the prevalence of smoking. D.M. Parkin et al. (2001) *Eur J Cancer* 37 Suppl. 8: S4 - 66.
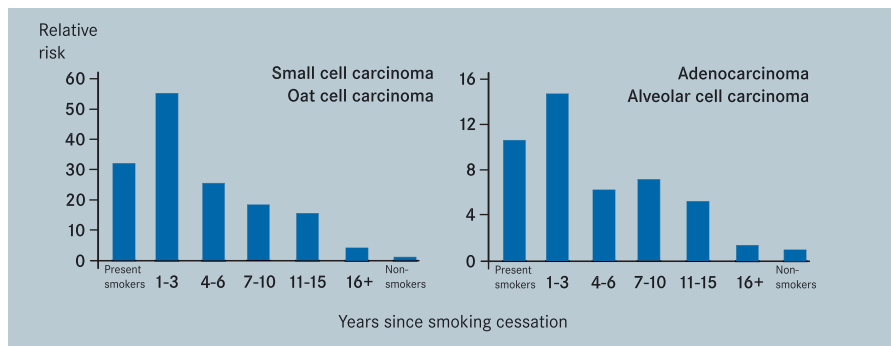
Fig. 5.5 The relative risk of lung cancer is markedly lower five years after quitting, and decreases further with time (by comparison with those who continue to smoke).
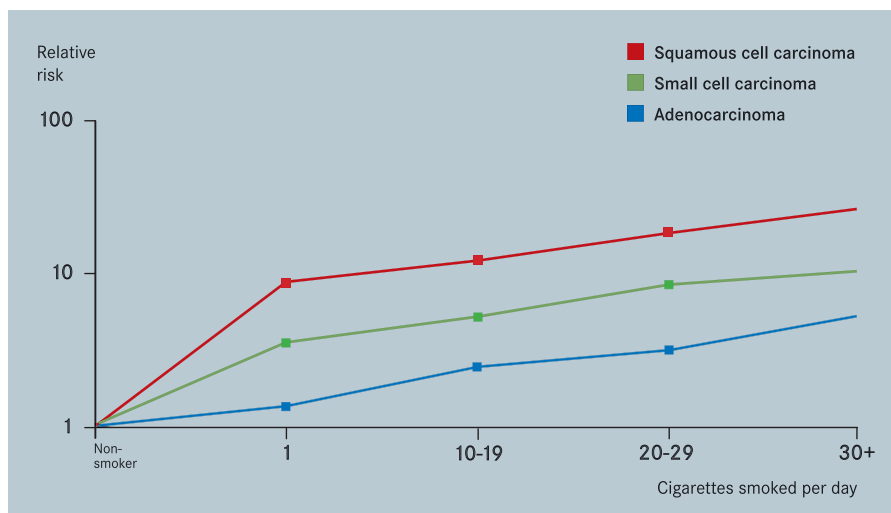

Fig. 5.6 The relative risk of major histological types of cancer by average cigarette consumption.

of lung cancer. Although the magnitude of the increased risk is moderate (relative risk, 1.5 to 2 for cumulative exposure in excess of 100 rads), the number of extra cases of lung cancer exceeds that of other neoplasms. Underground miners exposed to radioactive radon and its decay products have been found to be at an increased risk of lung cancer [5,6]. Indoor exposure to radon has been associated with a marginal increase in risk of lung cancer.

There is abundant evidence that lung cancer rates are higher in cities than in rural settings [7]. Urban air pollution is a risk factor for lung cancer and the excess risk may be in the order of 50% (*Environmental pollution*, p39). Two particular sources of indoor air pollution are the use of coal-burning heaters without proper exhaust emission (e.g. *kang* in North-Eastern China) and high-temperature cooking using unrefined vegetable oils, such as rapeseed oil (common in several parts of China). Indoor levels of benzo[a]pyrene have been reported to be very high in such circumstances [8]. Indoor air pollution is a major cause of lung cancer in Chinese women, who experience very high lung cancer rates despite a low prevalence of smoking.

There is convincing evidence that a diet rich in vegetables and fruits exerts a protective effect against lung cancer [9]. Subjects in the categories of highest consumption experience about 50% of the risk of lung cancer compared with subjects in the categories of lowest consumption.

Detection

Sputum cytology and radiology (chest X-ray and computed tomography (CT)) scans are the only non-invasive methods of detecting early lung cancer. Sensitivity can be variable dependent on histological type (greater for small cell and squamous cell carcinomas), tumour size and location [10]. Sputum cytology may be appropriate for certain clearly defined groups or individuals at risk of lung cancer. Currently, however, there are no practicable and effective procedures available to provide population-based screening for lung cancer.

The signs and symptoms of lung cancer depend on the location of the tumour, the spread and the effects of metastatic growth. Many patients are diagnosed on the basis of an asymptomatic lesion discovered incidentally on X-ray. Symptoms indicative of the primary tumour include fatigue, decreased activity, persistent cough, laboured breathing, chest pain, decreased appetite and weight loss. Hoarseness as a result of recurrent laryngeal nerve injury may be provoked by left-sided lesions, and superior vena cava syndrome by right-sided lesions. Wheeze or stridor may also develop in advanced stages. Continuous tumour growth may result in collapsed lung, pneumonia and abscess formation.

In some patients with lung cancer, metastatic deposits lead to the first symptoms; the majority of patients with lung cancer already have locally advanced disease or distant metastases at diagnosis; common metastatic sites are mediastinal and supraclavicular lymph nodes, liver, adrenal glands, brain, lungs, pleura and pericardium. Less commonly, a patient may be diagnosed on the basis of a paraneoplastic syndrome (signs and symptoms not produced by the direct effect of a tumour or its metastasis), such as the syndrome of inappropriate secretion of antidiuretic hormone in small cell lung cancers. Diagnostic procedures involve chest X-ray, bronchoscopy and sputum analysis, as well as CT and magnetic nuclear resonance. CT imaging is used for the detection of liver and adrenal gland metastases. Clinical and image-based

diagnosis is usually confirmed by histological examination of biopsies obtained by fibre-optic endoscopy or surgical specimens. Percutaneous fine needle aspiration may be used to diagnose peripheral tumours, or in the event of inconclusive bronchoscopy results. The complementary use of spiral CT in screening may improve the robustness with which lung cancer of any cell type can be detected early [11]. However, many cases of lung cancer, especially at older ages and in low resource countries, are diagnosed only on the basis of clinical and X-ray evidence.

Pathology and genetics

Principal histological types of lung cancer are squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma. The first three are also referred to as "non-small cell" lung carcinomas. In North America and Europe over the last 20 years, the proportion of squamous cell carcinoma, previously the predominant type, has been decreasing, while an increase of adenocarcinoma has been recorded in both genders. Squamous cell carcinoma arises most frequently in proximal segmental bronchi and is associated with squamous metaplasia. This tumour type is very strongly associated with smoking and represents the most common type of lung cancer in many populations. It tends to grow slowly, three to four years being required for development from an *in situ* lesion to a clinically apparent tumour. Adenocarcinoma is less strongly associated with smoking. This tumour is often peripheral in origin and may present as a solitary peripheral nodule, multifocal disease, or a rapidly progressive pneumonic form, spreading from lobe to lobe. These tumours form glands and produce mucin. Early metastasis is common, particularly to the brain, pleura and adrenal glands. Large cell carcinoma often appears in the distal bronchi and is generally undifferentiated. Small cell carcinoma typically arises in the central endobronchial location and is commonly aggressive and invasive; frequently metastases are present at diagnosis.

Although the histogenesis and the putative precursor lesions of lung cancer are largely unknown for the different histological types, the presence of putative precursor lesions (dysplasia, metaplasia and carcinoma *in situ*) are commonly reported in resection specimens and/or cytology for squamous cell carcinoma [12].

A positive familial history of lung cancer has been identified as a risk factor. Increased risk of lung cancer has been associated with certain polymorphisms of the cytochrome P450 genes and with deficiencies in DNA repair capacity [13]. Genetic changes associated with progression of premalignant lesions to malignant tumours have been identified [14] (Table 5.1). Mutations in the *p53* gene are frequent events in lung cancer, although adenocarcinoma shows a lower prevalence of *p53* mutations than other histological types. Among lung cancer cases, the proportion of *p53* mutations increases with duration and amount of tobacco smoking. A wide distribution and a variety of types of *p53* mutation have been observed following different environmental exposures; their analysis is likely to elucidate different mechanisms involved in lung carcinogenesis [15].

Activating point mutations in the *KRAS* oncogene (mainly at codon 12) occur in adenocarcinoma, with a prevalence ranging from 15% to 60%. This alteration, which is more prevalent in tumours from smokers than from non-smokers, may be a relatively early event in lung carcinogenesis. Frequent loss of heterozygosity and aber-
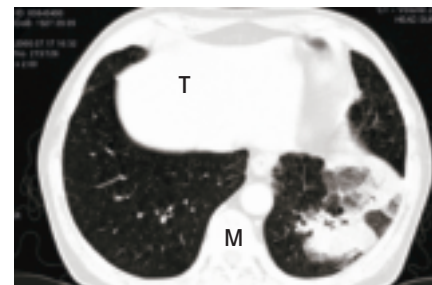

Fig. 5.7 A lung tumour viewed by computed tomography. T= tumour, M= mediastinum.
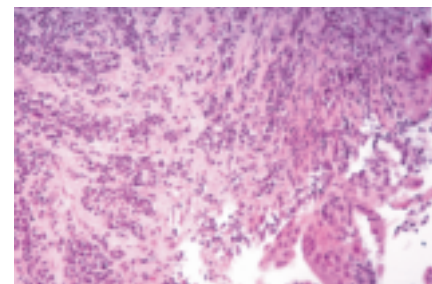

Fig. 5.8 Biopsy of a small cell lung carcinoma, showing a monomorphic proliferation of small tumour cells with dense nuclei and poorly-defined cytoplasm, invading the deep parts of the bronchial wall.
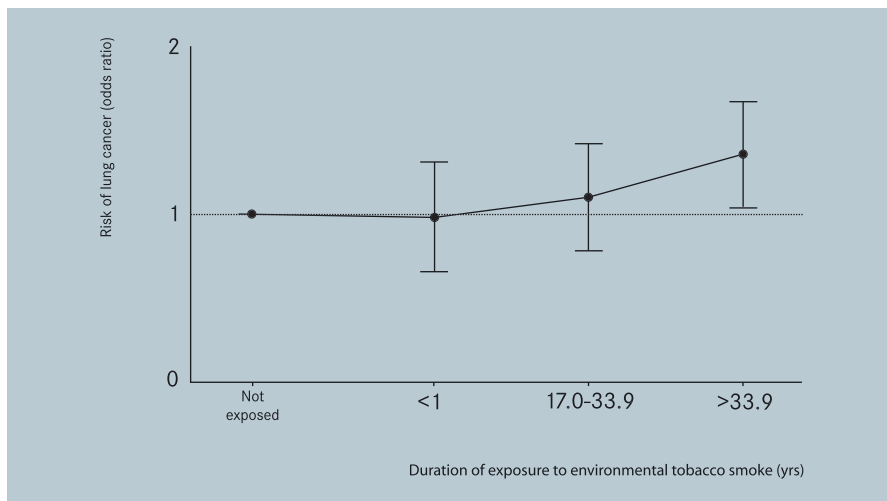

Fig. 5.9 Relative risk of lung cancer (odds ratio) among non-smokers by cumulative exposure to environmental tobacco smoke from the spouse and workplace. Pooled analysis of data from two studies in the USA and in Europe.

Fig. 5.10 Five-year relative survival rates of lung cancer patients after diagnosis.

rant transcripts of the Fragile Histidine Triad (*FHIT*) gene, located at chromosome 3p14.2, occur in pre-neoplastic and neoplastic lesions and such changes have been linked to smoking and asbestos exposure. Homozygous deletions and transcriptional silencing due to methylation in the locus of the cyclin-dependent kinase inhibitor p16^{INK4A} on chromosome 9p have been found in about 40% of lung cancer cases. Other oncogenes have also been implicated in lung carcinogenesis: in particular, *ERBB1* and *ERBB2*; *C-MYC*, *N-MYC* and *L-MYC*, and *BCL2* [16]. No clear correlations have been established as yet between particular genetic changes and histological type of tumour.

Management

Staging of lung cancer is based on an assessment of the presence of distant metastases and the condition of the chest and mediastinum (the tissues and organs separating the lungs), in accordance with the universally used TNM system (Box: *TNM*, p124). Although treatment protocols are subject to refinement and improvement, the outlook for patients diagnosed with lung cancer is poor by comparison with many other cancers. The main prognostic factors are stage of the tumour and performance status; other important factors include amount of weight loss, gender (men having a poorer prognosis than women), serum concentration of lactate dehydrogenase and the detection of bone and liver metastases.

Non-small cell carcinomas are grouped together because of similarity in the response of the different subtypes to treatment. Early stage tumours are treated by surgical resection, if possible, with patients who refuse or who are deemed medically unfit for surgery being treated with radiotherapy. More advanced stage disease may be treated with a combination of surgery and radiotherapy. Radiotherapy can be effective for palliation of superior vena cava obstruction, haemoptysis (expectoration of blood), pain, dyspnoea (shortness of breath), brain metastases and atelectasis (partial or complete lung collapse) [17]. The introduction of cisplatin-containing drug combinations improves the rate of response to therapy, with accompanying moderate to severe toxicity. Combination chemotherapy (using cisplatin and etoposide, or mitomycin, vinblastine and cisplatin) with radiotherapy also seems to convey a survival advantage in patients with stage III disease. More recently, paclitaxel has shown significant activity when used as a single agent. Other drugs credited with response rates of at least 15% include gemcitabine, docetaxel and vinorelbine. The mainstay of treatment for small cell
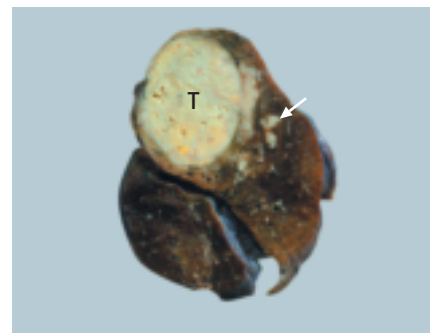

Fig. 5.11 A smoking-induced lung cancer. Autopsy specimen of a large-cell carcinoma of the left lung (T) with nearby metastases (arrow).

lung cancer is chemotherapy, with concomitant radiotherapy being used at an early point for patients with limited disease. Surgery may be considered in the case of a patient with a small isolated lesion [17]. Combinations of drugs, as a general rule, yield better results than the respective agents used alone and those commonly used include cisplatin and etoposide, cyclophosphamide, doxorubicin and vincristine, and cyclophosphamide, doxorubicin and etoposide. More recently, the taxanes paclitaxel and docetaxel and the camptothecins irinotecan and topotecan have shown promise as single agents and in combination. Despite good initial responses to therapy, relapse

Gene	Locus	Alteration	Frequency (% of tumours)		
			Small cell carcinoma	Adeno-carcinoma	Squamous cell carcinoma
p53	17p13	Deletion, mutation (G:C>T:A), (overexpression)	70-90	30	50
KRAS	12p21	Mutation (GGT>TGT)	<1	15-60	8-9
CDKN2A/ p16 ^{INK4}	9p21	Deletion, mutation, hypermethylation	<1	27-59	33-40
LOH 3p	3p	Deletion (loss of heterozygosity)	100	50-85	
FHIT	3p14.2	Deletion (loss of heterozygosity), transcriptional dysregulation	76	40-76	

Table 5.1 Genetic alterations in lung tumours.

is frequent and survival rates are poor (two-year survival of 20-30% for limited stage disease) although limited stage small cell cancer has a cure rate of about 10-15%. Treatment should be considered since good symptom control can be attained. Prophylactic cranial irradiation may reduce the risk of brain metastases, and has recently been shown in meta-analysis to prolong survival in limited small cell cancer.

Although survival for stage I cancers may reach about 65%, overall survival from lung cancer is poor (Fig. 5.10). In population-based series from high-income countries, the five-year relative survival barely exceeds 10%. However, survival is better among patients aged less than 55 at diagnosis (five-year relative survival in the order of 15%). There is evidence of a very modest improvement in survival during the last 20 years. In developing countries, survival rates are comparable to those in industrialized countries.

In the light of poor survival rates, prevention of lung cancer is a priority. However, the development of novel therapies remains important in view of the fact that most patients will die of disease progression and current treatments can be highly toxic. Trials of vaccination against tumour specific antigens such as carcinoembryonic antigen (CEA) and Fuc-GM1 are underway [18]. A further strategy under investigation is that of vaccination with tumour cells designed to have enhanced immunogenicity due to the expression of, for example, cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF).

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WEBSITE

NCI Lung Cancer Homepage:
http://www.cancer.gov/cancer_information/cancer_type/lung/

BREAST CANCER

SUMMARY

> Breast cancer is the most common malignancy affecting women, with more than one million cases occurring worldwide annually. Affluent societies carry the greatest risk, with incidence rates of >80 per 100,000 population per year.

> The worldwide breast cancer epidemic has many etiological factors, including reproductive history (early menarche, late or no pregnancy), and Western lifestyle (high caloric diet, lack of physical activity).

> In some regions, including North America, Western Europe and Australia, breast cancer mortality rates have started to decline, mainly due to improvements in early detection and treatment (chemotherapy and tamoxifen). Five-year survival rates are higher than 70% in most developed countries.

> Breast cancer screening trials of mammography have shown that mortality can be reduced by up to 30%. However, there is limited evidence that this can be achieved in population-based country-wide screening programmes.

Definition

Breast cancer generally refers to a malignancy in women that arises from the terminal ductal-lobular units of epithelial tissue, which in the mature breast represent 10% of the total volume.

Epidemiology

Latest estimates suggest that more than 1,050,000 new breast cancer cases occur worldwide annually, with nearly 580,000 cases occurring in developed countries and the remainder in developing countries [1]. Thus breast cancer now ranks first among cancers affecting women throughout the world and its marked impact is not restricted to Western industrialized societies (Fig. 5.12).
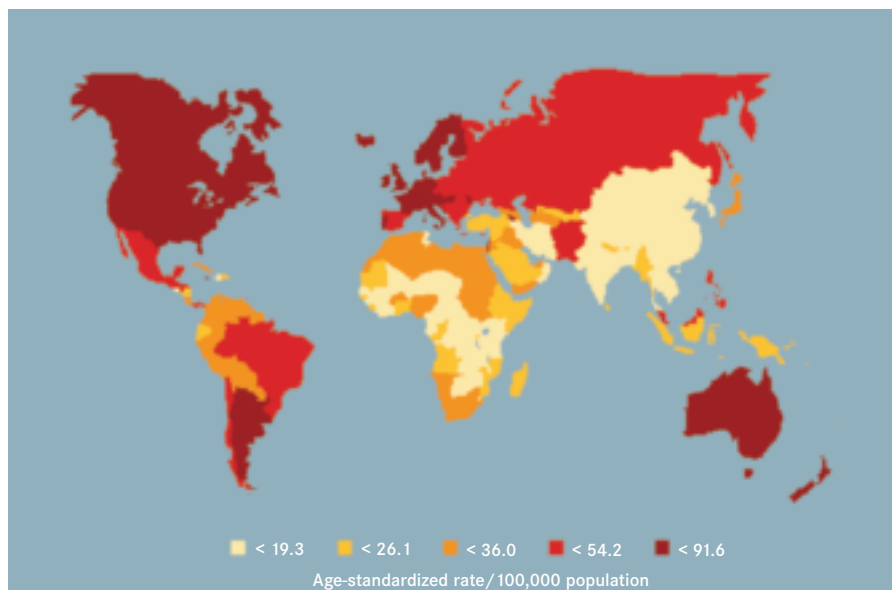

Fig. 5.12 The global burden of breast cancer in women; incidence is high in developed countries such as the USA, UK and Australia.

< 19.3   < 26.1   < 36.0   < 54.2   < 91.6
Age-standardized rate / 100,000 population

In 1998, there were 412,000 deaths attributed to breast cancer for women in the world, representing 1.6% of all female deaths. In terms of absolute numbers, the greatest contribution is now from developing countries, where 250,000 such deaths occurred, as compared to developed countries, which account for 160,000 deaths. However, the proportion of deaths due to breast cancer in women remains higher in the latter countries at 2.0% in comparison to 0.5% in the developing countries. Male breast cancer is about 100 times less frequent than the disease in women.

The Netherlands exemplifies the high incidence of breast cancer in developed countries, with an age-standardized incidence rate of 91.6 new cases per 100,000 woman-years, but there are sub-populations, such as white women in California, which exhibit age-adjusted incidence rates of 100 or more. Overall, the incidence rate in the USA is estimated at 91.4. Such high rates are also observed in Europe, Australia and New Zealand, and in

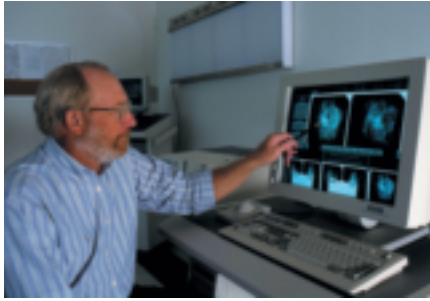Fig. 5.13 Risk of breast cancer is decreased in women who have children early and who have breast-fed.

Fig. 5.14 Physician reading digital images of the breast in preparation for a computer-guided minimally invasive biopsy.

some parts of South America, especially Uruguay and Argentina. In contrast, low rates are found among African and Asian populations. Amongst population-based cancer registries (as distinct from national estimates), the 30 recording the highest rates include 20 registries from North America, one from South America (Montevideo), two from Israel and five from Europe. Amongst this group, the only one from Africa is for Europeans in Harare. By contrast, among population-based registries with the 30 lowest rates, five are from Africa, 18 from Asia and Israel, three from South America, two from Eastern Europe and two from the United States of America (American Indians in New Mexico and Koreans in Los Angeles, California) [2].

These large geographical differences are potentially explicable on the basis of genetics or the influences of lifestyle and environment. Studies of migrant populations have revealed that when women migrate from low-risk to high-risk regions, the migrant populations acquire the rates of the host country after two or three generations, indicating lifestyle as primarily determining the geographic variations in risk.

"Cumulative incidence" represents the probability of developing a particular disease over a life span. Given the uncertainties of breast cancer diagnosis in older women and the high likelihood of the disease not being reported in the oldest age groups, it is common practice to present cumulative incidence for the age span 0-74 years. In the world, cumulative inci-

dences for breast cancer vary from 0.76% for women in Kangwha, Korea to 11.9% for non-Hispanic whites in San Francisco, USA [2].

The absolute number of new breast cancer cases worldwide increased from 572,100 in 1980 to 1,050,346 for the most recent period [3]. Comparison of rates rather than absolute figures excludes change attributable to ageing of the population as well as differences in age structures across countries. Even so, most cancer registries of the world have recorded an increase in the incidence of breast cancer over the past 20 years (*Screening for breast cancer*, p156). In the period 1975-1990, the largest increases, greater than 1% and sometimes 5% per year, are exhibited by registries previously having low rates of disease, mostly in Asia and Africa, as well as in some parts of Europe. In contrast, the smallest increases, in general inferior to 0.5% per year, are usually seen in places previously having high rates, mostly in North America and Europe. These changes are particularly obvious in relation to disease in younger women, that is below 45 years of age [2,4]. However, mortality rates are falling, probably due to better treatment (Fig. 5.19).

Etiology
Risk factors for breast cancer (Fig. 5.18) specifically concern the reproductive life of women. Increased risk is correlated with early menarche, nulliparity or late age at first birth, late menopause, as well as hormonal factors, be they endogenous or exogenous (e.g. long term use of oral contraceptives or menopausal hormonal replacement, *Reproductive factors and hormones*, p76). Genetic risk factors are discussed later (Pathology and genetics). Other risk factors that may also be mediated through a hormonal pathway include obesity and diet, characterized by a high caloric intake, not counterbalanced by sufficient physical activity, high total and saturated animal fat, as well as a diet poor in fruits and vegetables and rich in meat and alcohol [5,6]. The role of contaminants, such as xenoestrogens and certain pesticides, remains controversial. Radiation, in
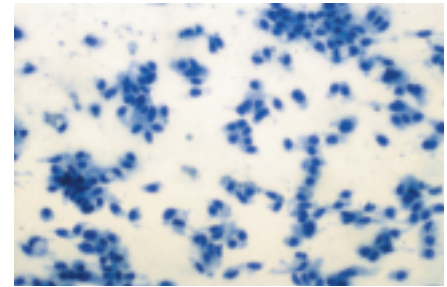

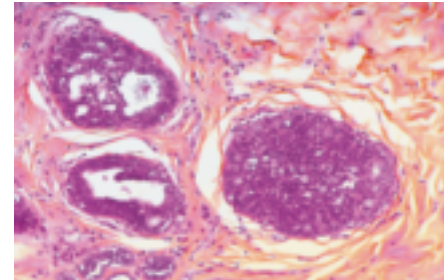Fig. 5.15 Fine needle aspirate of cells from a breast tumour.

Fig. 5.16 An example of lobular carcinoma *in situ*, comprising a well-differentiated malignant proliferation without signs of invasion.
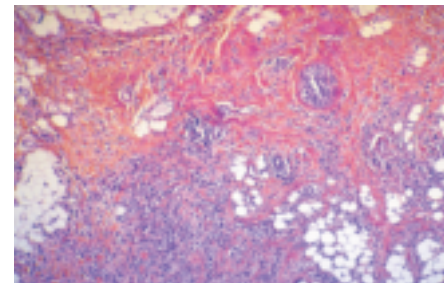

Fig. 5.17 Infiltrating ductal carcinoma. This is a poorly-differentiated adenocarcinoma infiltrating the adipose tissue.

particular at times of breast development, causes breast cancer. Women with epithelial proliferative lesions, particularly with atypical ductal or lobular hyperplasia by comparison with normal histology, have a four to five times increase in the risk of developing breast cancer [7].

Detection
The commonest presentation of breast cancer is of a painless lump; other symptoms may include dimpling of the overlying skin, nipple inversion, oedema or *peau d'orange* and blood-stained nipple discharge. In countries where no mammo-
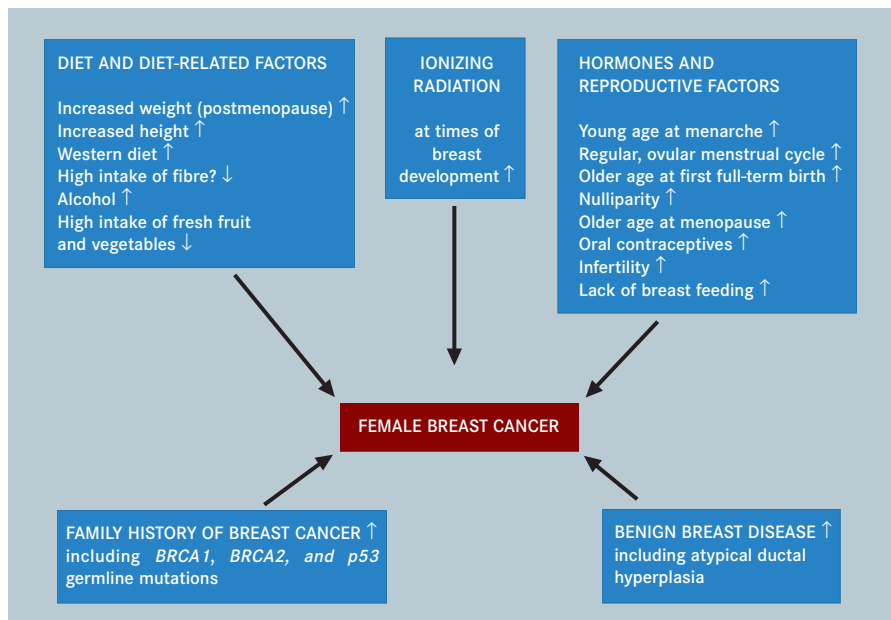
Fig. 5.18 Risk and protective factors for breast cancer. Factors associated with an increased (↑) or decreased (↓) risk of breast cancer.

A woman may be considered to be at a potentially high risk of breast cancer if there are three or more first or second degree relatives on the same side of the family with breast or ovarian cancer, or two or more first or second degree relatives on the same side of the family with breast or ovarian cancer which has been diagnosed at age 40 or younger, bilateral disease, both breast and ovarian cancer in the same individual or breast cancer in a male [11]. The currently available approaches to the management of the high-risk woman are close surveillance (involving regular self and clinical breast examination and annual mammography), genetic counselling or prophylactic mastectomy (a procedure which does not, however, guarantee complete prevention of subsequent breast cancer).

Pathology and genetics

Ductal carcinoma *in situ* is a proliferation of presumably malignant epithelial cells and is confined to the mammary ducts and lobules. It carries a 30% chance of developing into invasive disease, although the natural history of this progression remains uncertain. The rate of detection of ductal carcinoma *in situ* has increased significantly with the introduction of mammography and questions have been raised regarding the possible overtreatment of this condition. It can be classified into comedo and non-comedo subtypes based on growth pattern, the comedo

graphic screening exists, and in fact for women generally, health education should include recognition of breast cancer symptoms. Diagnosis of breast cancer is currently made by triple assessment of breast lumps – clinical history and examination, complemented by mammography and/or breast ultrasound plus fine needle aspiration cytology or biopsy [8]. Breast screening can have an impact on disease

mortality. Mammography is associated with a reduction of up to 30% in breast cancer mortality in the context of well-conducted trials [9]. Where adopted, population-based screening is commonly based on biennial examination from the age of 50 onwards. To realize the benefit of screening, prompt and adequate follow-up must be available to all women with a suspected malignancy [10].
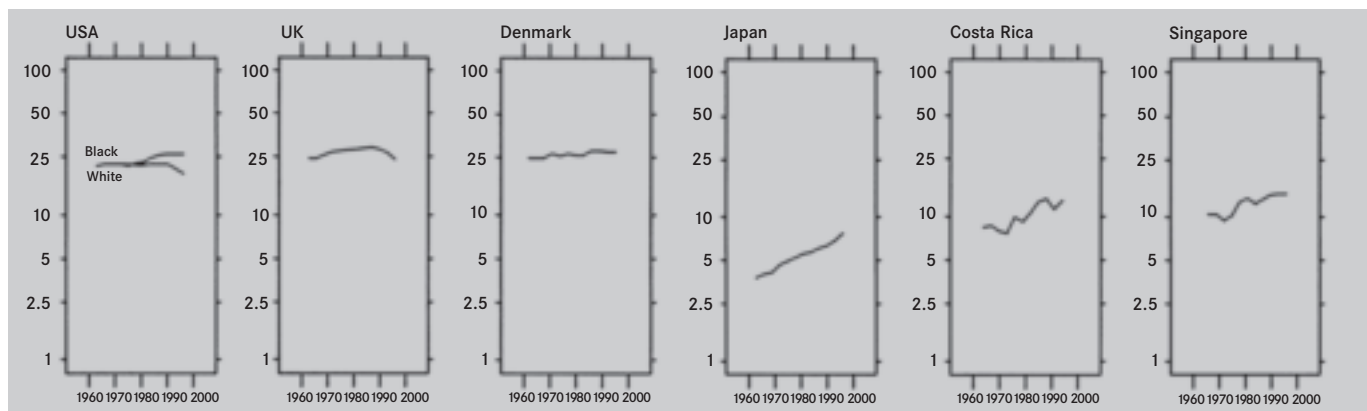

Fig. 5.19 Trends in mortality from breast cancer. In some countries, such the USA and UK mortality is decreasing; in almost all developing countries, mortality is increasing. D.M. Parkin et al. (2001) *Eur J Cancer* 37 Suppl 8: S4-66

Commonly assessed markers:
Number of positive axillary lymph nodes
Tumour size
Tumour TNM stage
Lymphatic and vascular invasion
Histological tumour type
Steroid hormone receptors (estrogen receptors ER-α, ER-β; progesterone receptor)
Growth factor receptor genes (epidermal growth factor gene, *EGFR*)
DNA ploidy (DNA histogram)
Proliferative indices (fraction of cells in S-phase; thymidine labelling index; mitotic index)

Less commonly assessed markers:
Proliferative indices (Ki67, PCNA, cyclins, thymidylate synthetase, MIB1)
Topoisomerase II
Histone H3
Transforming growth factors (TGF-α, TGF-β)
Epidermal growth factor (EGF)
Insulin-like growth factors and their binding proteins (IGF-I, IGF-II)
Oncogene products (c-erbB2, ras, c-myc, int2)
Markers of apoptosis (mutations of p53, Bcl-2 proteins, caspases, survirin, p21, R6)
Markers of proteolysis (activation of urokinase-type plasminogen, cathepsin D, matrix metalloproteases)
Markers of cell adhesion (integrins, cadherins, CD-44 variants)
Markers of angiogenesis (endothelial markers: Factor VII, CD-31, CD34; angiogenic peptides e.g. VEGF)
Markers of cell mobility (cytokines)
Steroid hormones (estrogens, glucocorticoids, prolactin, progestins)
Tumour-associated antigens (carcinoembryogenic antigen, CEA; tissue polypeptide antigen, TPA; gross cystic disease fluid protein, GCDP; mucin-like molecules, CA 15.3, MAM-6, MSA, MC)
pS2
NM23
Heat shock proteins
MDR1

Table 5.2 Prognostic indicators in breast cancer.

Fig. 5.20 Physician performing a sentinel lymph node biopsy. With this state-of-the-art radio-guided surgical equipment, the patient avoids complete resection of the axillary lymphatic nodes and the complications of lymphoedema.
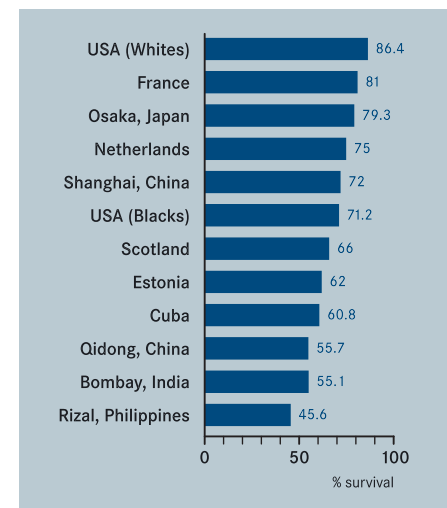

Fig. 5.21 Five-year relative survival rates after diagnosis of breast cancer.

type, having a higher rate of proliferation, being more aggressive and more likely to be associated with areas of microinvasion and with expression of markers such as aneuploidy and overexpression of p53, c-erbB2 and Bcl-2. Lobular carcinoma *in situ* (Fig. 5.16), unlike ductal carcinoma *in situ*, is not readily detected clinically or mammographically, is frequently multicentric and bilateral, and occurs more commonly in younger women. It is associated with an increased risk for development of cancer, but is not a precursor lesion. Lobular carcinoma *in situ* is characterized by a solid proliferation of small cells with small uniform, round or oval nuclei, which grow slowly, are usually estrogen receptor positive and rarely overexpress c-erbB2. The most frequent malignant lesion (80%) is invasive ductal carcinoma of no special type, with 20% of cancers being lobular, tubular, medullary or other special types (Fig. 5.17).

The most important genes identified in the context of familial breast cancer are *BRCA1* and *BRCA2* [12]. Inherited mutations in these genes account for a very high relative risk of breast and sometimes ovarian cancer among carrier women [13], although such instances of breast cancer account for less than 5% of all cases (*Genetic susceptibility*, p71). Other genetic conditions suspected of playing a role include heterozygosity of the ataxia telangiectasia gene (Box: *ATM and breast cancer*, p192) and germline mutations of *p53* (the Li-Fraumeni syndrome) [14].

The most common genetic abnormality in breast carcinoma tissue appears to be a loss of heterogeneity at multiple loci. Such change may determine the influence of a mutated allele of a tumour suppressor gene (*Oncogenes and tumour suppressor genes*, p96). Loss of heterogeneity on 13q and 17p may involve the *RB* or *p53* genes respectively. Gene amplification is also observed, the most studied gene in this context being that encoding the growth factor receptor c-erbB2. Although the estrogen receptor cannot be clearly classified as the product of an oncogene or tumour suppressor, expression of this gene mediates progression of breast cancer, and the responsiveness of tumours to hormone-based therapy.

Management
Successful management of a breast cancer implies a multidisciplinary approach to

ATM AND BREAST CANCER

Whilst mutations in the *BRCA1* and *BRCA2* genes contribute to familial breast cancer risk, their contribution to sporadic breast cancer is relatively minor. In the latter disease category, genes frequently altered in the general population, such as the gene mutated in ataxia telangiectasia, *ATM*, may be important risk factors. Studies of ataxia telangiectasia families initially revealed that ataxia telangiectasia heterozygotic women had an increased risk of breast cancer. Taken together with the estimation that 1% of the general population are *ATM* heterozygotes, up to 8% of breast cancer patients could thus be *ATM* heterozygotes. One of the identifying characteristics of ataxia telangiectasia patients is that they are extremely sensitive to ionizing radiation. Radiosensitivity, seen as exaggerated acute or late tissue reactions after radiotherapy, has been reported in a significant proportion of breast cancer patients. This suggests that ataxia telangiectasia heterozygosity plays a role in such radiosensitivity and in breast cancer development. Loss of heterozygosity in the region of the *ATM* gene on chromosome 11 has been found in about 40% of sporadic breast tumours. Screening for *ATM* mutations in sporadic breast cancer cases, regardless of adverse response to radiotherapy, has not
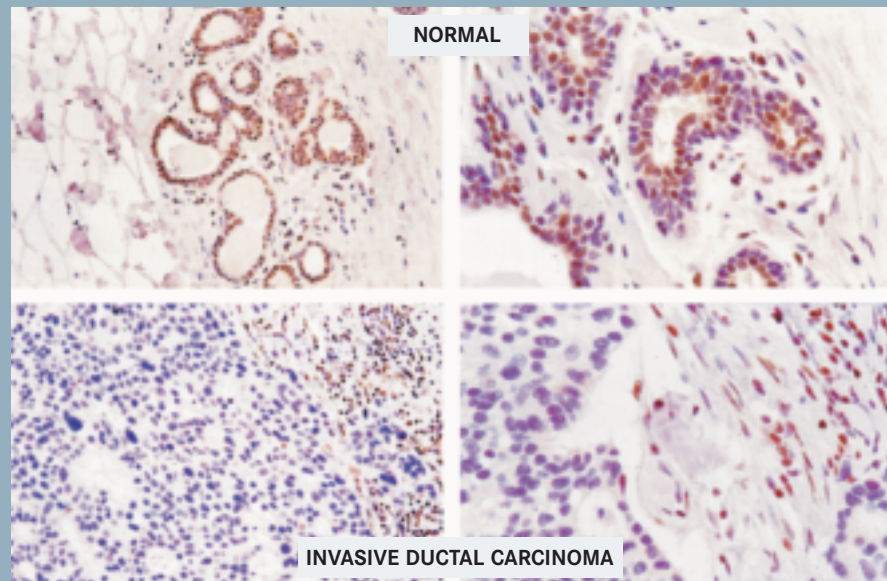

Fig. 5.22 Normal tissue showing a brown nuclear ATM staining in the inner epithelial cells of the breast ducts and no staining in the outer myoepithelial cells. Invasive ductal carcinoma shows no ATM staining in the tumour area, in contrast to lymphocytes in the same section.

revealed the magnitude of involvement of the *ATM* gene expected, based on the increased relative risk and mutation profile found in family studies (in terms of truncating mutations). However, the molecular approaches used in these studies have shown clearly that, in the general population, there are two groups of heterozygotes (Gatti RA et al., *Mol Genet Metab*, 68: 419-422, 1999). One group includes those who are heterozygous for a truncating allele and a second group comprises those who are heterozygous for a missense mutation; the latter group might predominantly include those individuals who are predisposed to developing sporadic cancers. Further research, in particular on the role and phenotype associated with these rare *ATM* sequence variants, is needed to clarify the understanding of *ATM* heterozygosity as a risk factor for breast cancer.

achieve local disease control (surgery and radiotherapy) and treat metastatic spread (chemotherapy) [15]. Optimal surgery may comprise a lumpectomy for a tumour of <4 cm, or mastectomy and excision of axillary lymph nodes for more advanced disease and depending on pathological findings [16]. Biopsy of the first lymph node to which a tumour drains ("sentinel node biopsy") is currently being investigated as an alternative to complete axillary lymph node dissection (which may be associated with post-surgical complications such as lymphœdema, numbness, a persistent burning sensation, infection, and limited movement of the shoulder) [17]. In early stage disease, lumpectomy followed by radiotherapy will allow for breast conservation. For larger tumours, a primary mastectomy may be necessary. Immediate or delayed breast reconstruction will allow for an acceptable cosmetic result, many techniques for which exist, including insertion of subpectoral silicone implants or tissue expanders and myocutaneous latissimus dorsi or rectus abdominous flaps (*Rehabilitation*, p292). There is no evidence that immediate reconstructive surgery prevents the detection of local recurrence or affects survival. Surgical removal of a breast tumour should be followed by radiotherapy to the breast. There is no difference in long-term disease control between mastectomy and complete local resection plus radiotherapy to reduce the incidence of local recurrence. In addition to local therapy, systemic adjuvant therapy, which may involve hormonal manipulation, including ovarian ablation and cytotoxic agents, is employed to treat undetectable remaining malignant cells. Ovarian ablation, whether achieved surgically or pharmacologically, is appropriate only for premenopausal women. The non-steroidal anti-estrogen drug tamoxifen is probably the single mostly widely-used agent for all stages of breast cancer, though it is more effective in women whose tumours exhibit estrogen receptors. Tamoxifen also substantially reduces the risk of a new primary breast can-

cer in the contralateral breast (*Chemoprevention*, p151), a property not seen with cytotoxic adjuvant therapy. In postmenopausal women who have had breast cancer, tamoxifen can reduce the annual rate of death by 17%. However, long-term use has been associated with endometrial thickening and endometrial carcinoma. A new-generation hormonal drug, anastrozole, has recently been reported to be just as, if not more, effective than tamoxifen in treating advanced breast cancer and as adjuvant therapy.

The strongest predictive factor for survival after diagnosis of breast cancer is the extent of cancer as defined in the TNM classification

(Box: *TNM*, p124). If the tumour is large, diffuse or multicentric, mastectomy may be appropriate. Involvement of axillary lymph nodes is an indicator of high risk of relapse from metastatic disease. An increasing number of molecular markers of prognosis are also becoming commonly assessed (Table 5.2) [14]. Metastatic disease is incurable; once detected, average survival time is two years. However, at least half the patients with breast cancer will survive for five years, including those living in the developing world. Because of this relatively good prognosis, there are an estimated 3.46 million women alive who have had breast cancer diagnosed

within the last five years. In Europe for example, survival is an average of 72.5% at five years (Fig. 5.21).

Patient follow-up involves the diagnosis and treatment of recurrent disease, evaluation of treatment effectiveness, monitoring for long-term complications, patient rehabilitation and psychological support. The combination of various treatment modalities has led to an improvement in survival for the last 20 years. The challenge remains of also providing adequate treatment in the developing world.

CLASSIFYING CANCERS: EPIDEMIOLOGICAL AND CLINICAL NEEDS

To monitor the impact of cancer within populations, epidemiological records are based on organ site (topography), liver cancer, breast cancer, colon cancer etc, using established codes (*International Classification of Disease*, see http://www.cdc.gov/nchs/about/otheract/icd9/abticd10.htm). Accordingly, this terminology applies to Chapters 1 and 2 of this Report.

To describe the type of cancer (or tumour) affecting an individual in terms which will

indicate the prognosis and appropriate treatment, reference to organ site alone is inadequate. For clinical purposes, tumours are identified by a naming system based on the tissue or cell of origin. All organs involve multiple tissue types including glandular or secretory tissue, connective tissue of various types (muscle, fat), blood and immunological elements and nervous tissue. "Carcinoma" indicates a malignant tumour of surface or glandular tissue, "sarcoma" indicates connective tissue, "blastoma" indicates embryonic tissue, "leukaemia" involves elements of blood and there are other specialist terms. Of necessity, Chapters 5 and 6 of this Report

use this terminology. The existence of a standardized classification system is of key importance (*WHO Classification of Tumours*).

In practice, particularly in the context of broad generalizations about cancer, the complexity implicit in comprehensive tumour nomenclature is greatly reduced by the practical consideration that over 90% of the tumours afflicting humans are carcinomas. As a result, for many purposes (and often in common practice) "lung cancer" may be equated with "carcinoma of the lung".

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STOMACH CANCER

SUMMARY

> Cancer of the stomach is amongst the most common malignancies worldwide, with some 870,000 new cases every year. Mortality from stomach cancer is second only to lung cancer.

> Incidence is declining worldwide. In most European countries it has fallen by more than 60% during the past 50 years. This trend is mainly due to markedly decreased consumption of salt-preserved food, increasing avoidance of a high-salt diet and availability, in many countries, of fresh fruit and vegetables throughout the year.

> Infection with *Helicobacter pylori* causes chronic atrophic gastritis and is considered a factor in the development of stomach cancer.

> Patients are often diagnosed with advanced disease and five-year survival rates are poor, usually less than 30%.

Legend: < 5.9 | < 9.6 | < 14.6 | < 22.0 | < 70.0
Age-standardized rate/100,000 population

Fig. 5.23 Global incidence of stomach cancer in men; the highest rates occur in Eastern Asia, South America and Eastern Europe.

Definition

The vast majority of stomach cancer cases are gastric carcinomas. Non-epithelial tumours predominantly include lymphomas and mesenchymal tumours.

Epidemiology

Stomach cancer was the fourth most common malignancy in the world in 2000, with an estimated 870,000 new cases and 650,000 deaths per year [1]. Approximately 60% of all stomach cancers occur in developing countries (Fig. 5.23). The areas with the highest incidence rates (>40/100,000 in males) are in Eastern Asia, the Andean regions of South America and Eastern Europe. Low rates (< 15/100,000) occur in North America, Northern Europe and most countries in Africa and in South Eastern Asia. There is 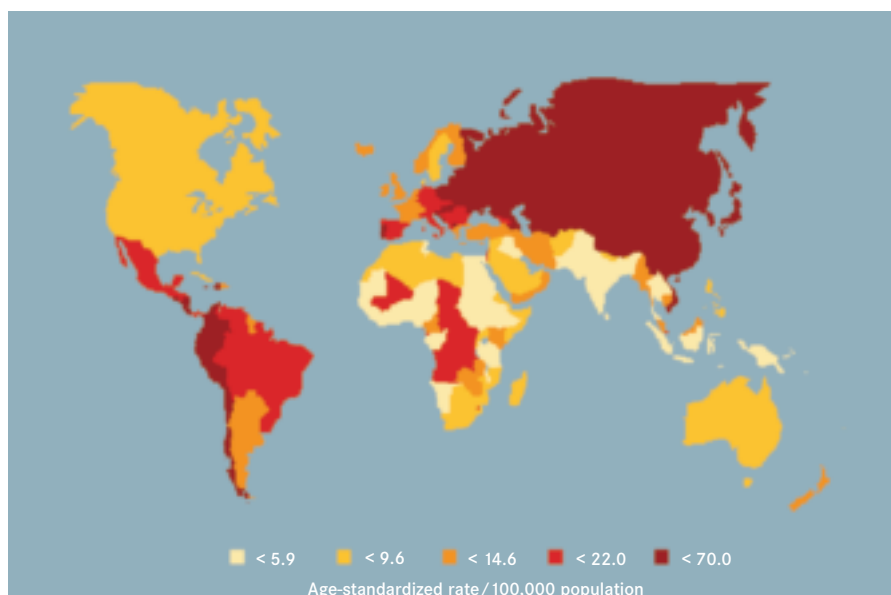marked geographical variation in incidence between countries and among different ethnic groups within the same locale. Migration studies show that the risk of cancer changes within two generations when people move from high-incidence to low-incidence areas. For example, Japanese immigrants to the USA retain their original risk of stomach cancer, whereas subsequent generations show the incidence of the host country. Incidence in men is twice that in women in both high- and low-risk countries.

The well-differentiated type of adenocarcinoma (which is showing the greatest decrease in incidence) occurs more predominantly in high-risk areas, while the diffuse poorly-differentiated type is relatively more frequent in low-risk areas [2]. In contrast to the overall decreasing trend, there has been an increase of cancers localized to the cardia, documented by data from the UK and USA. The reasons for this increase are not known. Over the last few decades, a steady decline in the incidence and mortality rates of gastric carcinoma has been observed worldwide and in particular in North America and Western Europe (Fig. 5.24 and *Stomach cancer prevention and screening*, p175). However, the absolute number of new cases per year is increasing mainly because of ageing of the population. Gastric carcinoma is extremely rare below age 30; thereafter incidence increases rapidly and steadily to reach the highest rates in the oldest age groups in both sexes.

Etiology

Dietary risk factors include inadequate intake of fresh fruits and vegetables, high salt intake and consumption of smoked or cured meats or fish. There is good evidence that refrigeration of food also protects against this cancer by facilitating year-round consumption of fruit and vegetables and probably by reducing the need for salt as a preservative. Vitamin C, contained in vegetables and fruits and other foods of plant origin, is probably protective, and so too are diets high in wholegrain cereals, carotenoids and allium compounds, and also green tea. Conversely,
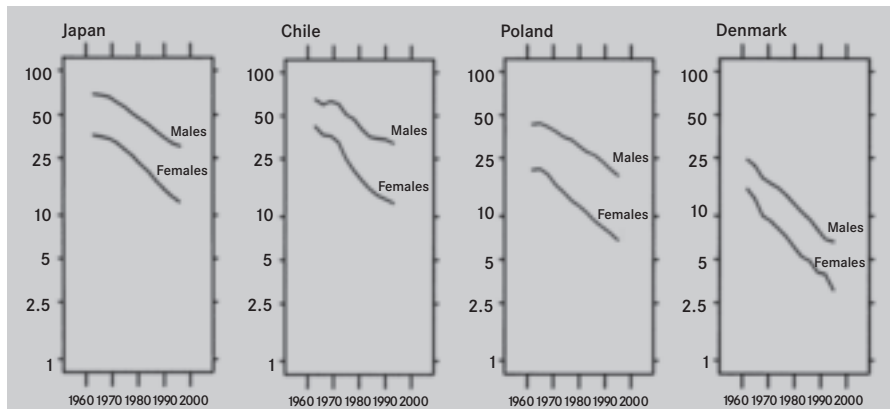
Fig. 5.24 The mortality from stomach cancer is decreasing worldwide, including in countries with a high disease burden. D.M. Parkin et al. (2001) *Eur J Cancer*, 37 Suppl. 8: S4-66.

monotonous diets which are rich in starchy food pose an increased risk, probably because they are deficient in the protective dietary constituents. Many studies suggest a small increase in risk (about two-fold) in smokers, but alcohol does not affect risk, other than at the gastric cardia. Conditions which cause an excessive rate of cell proliferation in the gastric epithelium, thus increasing the chance of fixation of replication errors induced by dietary and endogenous carcinogens, include *Helicobacter pylori* infection (*Chronic infections*, p56), gastric ulcer, atrophic gastritis and autoimmune gastritis associated with pernicious anaemia. Gastritis is associated with increased production of oxidants and reactive nitrogen intermediates, including nitric oxide. There is increased expression of the inducible isoform of nitric oxide synthase in gastritis. Gastritis and atrophy alter gastric acid secretion, elevating gastric pH, changing the gastric flora and allowing anaerobic bacteria to colonize the stomach.

Detection

Early stomach cancer is an adenocarcinoma limited to the mucosa, or the mucosa and submucosa. It often does not cause symptoms, although up to 50% of patients may have non-specific gastrointestinal complaints, such as dyspepsia. This often delays the diagnosis of stomach cancer. Approximately 80% of Western patients with stomach cancer present to the physician with advanced tumours, symptoms of which may include nausea, weight loss, back pain, epigastric pain, gastrointestinal bleeding or perforation [3]. Endoscopy and biopsy is considered to be the most sensitive and specific diagnostic test for stomach cancer. Endoscopic detection of early lesions may be improved with dye-endoscopy using indigo carmine, congo-red, truigine or methylene blue. Diagnosis may also be obtained by double-contrast barium X-ray. Screening for early disease by X-ray (photofluoroscopy), followed by gastroscopy and biopsy of suspicious findings, has been widely used in Japan since the 1960s. It is a costly approach to prevention, and the results have been controversial. Serum pepsinogen screening is a new and potentially useful method for detection of stomach cancer [4].

Tumour staging prior to treatment decision involves percutaneous ultrasound or computed tomography to detect liver metastases and distant lymph node metastases and laparoscopy (with or without laparoscopic ultrasound) to seek evidence for peritoneal spread or serosal involvement.

Pathology and genetics

Chronic atrophic gastritis, in particular *H. pylori*-associated chronic active gastritis,
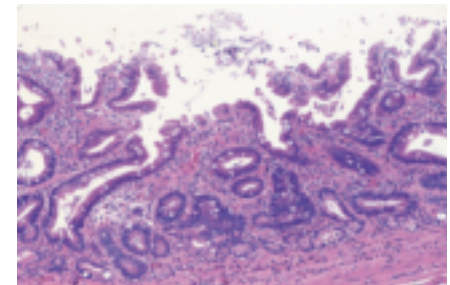

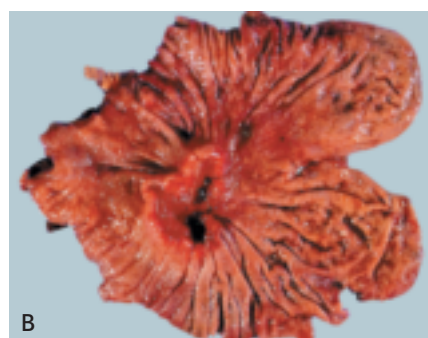Fig. 5.25 Severe atrophic gastritis with intestinal metaplasia, a risk factor for gastric carcinoma.

Fig. 5.26 (A) Endoscopy showing advanced gastric carcinoma in an 80-year-old male patient (ulcerated tumour without definite limits, infiltrating into the surrounding stomach wall). (B) Corresponding gross feature of the resected stomach with advanced cancer located in the lesser curvature of the angulus.
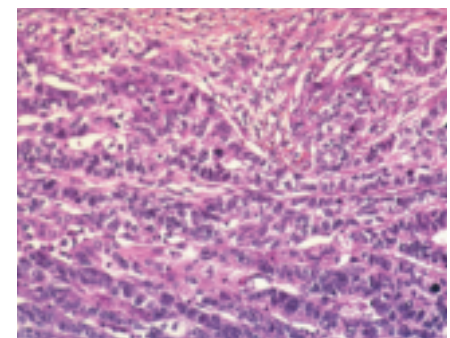

Fig. 5.27 Invasive gastric carcinoma: a well-differentiated trabecular invasive tubular adenocarcinoma.

Gene alterations	Histologic type	
	Poorly-differentiated (%)	Well-differentiated (%)
KRAS mutation	0	10-20
c-met Amplification 6.0 kb mRNA	≈40 ≈80	≈20 ≈50
K-sam amplification	20-30	0
c-erbB2 amplification	0	20-40
Cyclin E amplification	10	10
p53 LOH/mutation	≈80	≈60
APC LOH/mutation	-	40-60
DCC LOH	-	50
Cadherin, catenin deletion	50	-
CD44 abnormal transcript	100	100
Genetic instability	≈40	≈10

Table 5.3 Genetic alterations in gastric carcinomas, (≈ = approximately), [15, 16].

and intestinal metaplasia (Fig. 5.25), frequently precede and/or accompany intestinal type adenocarcinoma, especially in high incidence areas. Premalignant conditions include gastric polyps, Menetrier disease, gastric ulcer, pernicious anaemia (achlorydia) and previous gastric surgery to reduce acid output [3]. *H. pylori* strains containing a group of genes named *cag* induce a great degree of inflammation, and there is an association between infection with a *cag* positive *H. pylori* strain and the development of gastric carcinoma [5]. Gastric carcinomas are morphologically heterogeneous, resulting in various classifications based on histological appearance, degree of differentiation, growth pattern, and histogenesis [6]. The major histological types include tubular adenocarcinoma (Fig. 5.27), papillary adenocarcinoma, mucinous adenocarcinoma and signet-ring cell carcinoma. When more than one histological type is observed within the tumour, the diagnosis is based on the predominant histological pattern [7]. Based on their differentiation status, gastric carcinomas are also classified as well-differentiated adenocarcinoma (composed of well-formed glands, often resembling metaplastic intestinal epithelium) and poorly-differentiated adenocarcinoma (composed of highly irregular glands or single cells that remain isolated). Moderately-differentiated adenocarcinomas show intermediate features between the two.

Gastric carcinomas may also be classified as diffuse and intestinal types (Laurén classification) [8]. Intestinal type carcinoma is composed of distinct glandular elements with well-defined lumina, sometimes accompanied by papillary structures or solid components. Diffuse gastric carcinoma is characterized by the lack of cell cohesion, and malignant cells infiltrate the surrounding tissue as single cells or small clusters of cells without glandular lumina [8]. Other classification systems are also in use.

Clinical and pathological staging of stomach cancer is based on the TNM system (Box: *TNM*, p124) in Western countries and the Japanese classification system in Japan [9]. Most gastric carcinomas occur sporadically, but up to 10% have an inherited familial component [10]. Case-control studies also suggest a small but consistent increased risk in first-degree relatives of gastric carcinoma patients [11]. Germline E-cadherin (*CDH1*) mutations lead to an autosomal dominant predisposition to diffuse gastric carcinoma [12]. Gastric carcinomas may also develop as part of the hereditary non-polyposis colon cancer (HNPCC) syndrome [13] (*Colorectal cancer*, p198). They exhibit intestinal type cancers and microsatellite instability.

Loss of heterozygosity studies and comparative genomic hybridization (CGH) studies have shown that frequent loss or gain occurs at chromosomal regions 1p, 1q, 3p, 4, 5q (*APC* locus), 6q, 7q, 9p, 17p (*p53* locus), 18q (*DCC* locus), and 20q [14]. Well- and poorly-differentiated adenocarcinomas frequently show different genetic alterations (Table 5.3), as do diffuse and intestinal types [15,16].

Management

Most patients diagnosed with stomach cancer have advanced disease and the prognosis is extremely poor with survival rates rarely exceeding 15%. Differences in classification of cancer lead to apparently much higher survival rates in Japan (Fig. 5.28). Management of stomach cancer
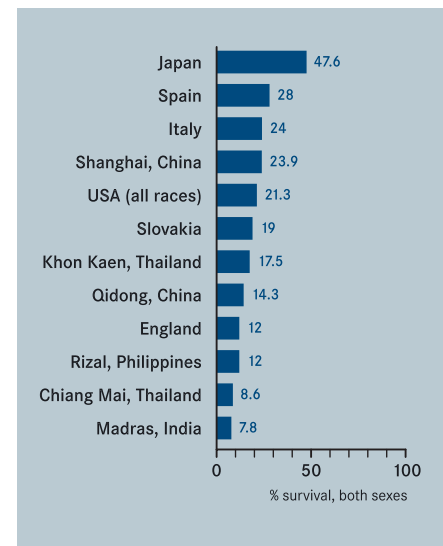

	% survival
Japan	47.6
Spain	28
Italy	24
Shanghai, China	23.9
USA (all races)	21.3
Slovakia	19
Khon Kaen, Thailand	17.5
Qidong, China	14.3
England	12
Rizal, Philippines	12
Chiang Mai, Thailand	8.6
Madras, India	7.8

% survival, both sexes

Fig. 5.28 Five-year relative survival after diagnosis of gastric carcinoma.

depends on staging. Small intramucosal cancers can be treated endoscopically by endoscopic mucosal resection [17]. For invasive cancer, standard treatment is gastrectomy with regional lymph node dissection [18]. For patients with advanced stage stomach cancer, neo-adjuvant (pre-operative) or adjuvant (post-operative) chemotherapy is currently being investigated in research protocols. Drugs most often employed are 5-fluorouracil, doxorubicin and cisplatin, and greatest success has been achieved on the basis of combination regimens rather than single agent treatments. Immunochemosurgery using

Corynebacterium parvum is practised in Korea, but is still subject to scepticism in Western practice [3].

Annual surveillance endoscopy, post-gastrectomy, has been associated with a small beneficial outcome in terms of gain of life-years, but this may be inflated by the exaggerated assumptions of a high incidence rate of gastric stump cancer and a cure rate of 80% achieved by timely surgery after cancer detection.

In advanced stomach cancer, tumour stage, tumour size, histological tumour type, growth pattern, degree of cytological atypia, DNA-nuclear content, stromal reaction, lymphatic and vascular invasion all have prognostic value. Patients with cancers limited to the mucosa and submucosa have a five-year survival of approximately 95%. Tumours that invade the muscularis propria have a 60% to 80% five-year survival, whereas tumours invading the subserosa and serosa have a less than 50% five-year survival on average [19]. There is recent evidence that the type of mucin and polymorphism of the gene encoding mucin may be an important factor determining susceptibility to stomach cancer [20].

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WEBSITE

NCI Stomach (Gastric) Cancer Homepage:
http://www.cancer.gov/cancer_information/cancer_type/stomach/

COLORECTAL CANCER

SUMMARY

> Cancers of the colon and rectum are rare in developing countries, but are the second most frequent malignancy in affluent societies; over 940,000 cases occur annually worldwide.

> A major etiological factor is lifestyle involving a diet rich in fat, refined carbohydrates and animal protein, combined with low physical activity.

> Studies suggest that risk can be reduced by decreasing meat consumption and increasing intake of vegetables and fruit.

> Sequential genetic alterations mediate development of colon cancer, the earliest such change being mutation of the *APC* gene.

> Familial clustering has usually a genetic basis. Typical syndromes include familial adenomatosis polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC).

> Colonoscopy is the most reliable means for early detection. Progressively improved treatment has resulted in a five-year survival rate of about 50%.

Fig. 5.29 Global incidence of colorectal cancer in women. Incidence rates are highest in North America, Western Europe and Australia/New Zealand.

Definition

The majority of cancers occurring in the colon and rectum are adenocarcinomas, which account for more than 90% of all large bowel tumours.

Epidemiology

Colorectal cancer ranks second in terms of both incidence and mortality in more developed countries. Nearly 945,000 new colorectal cancer cases are diagnosed worldwide each year and colorectal cancer is responsible for some 492,000 deaths. There is significant geographical variation in age-standardized incidence as we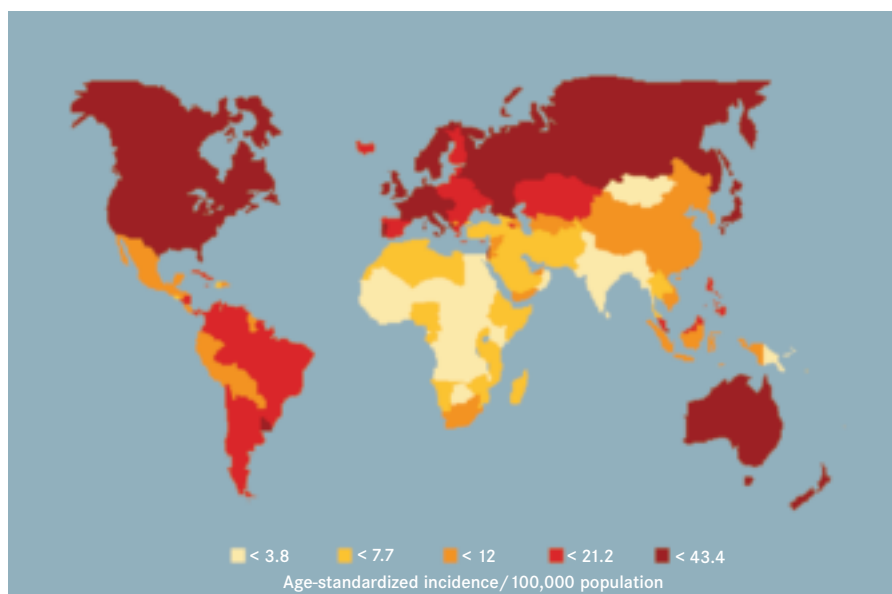ll as in cumulative 0-74 year incidence, high rates occurring in countries of Europe, North America, in Australia and, more recently, in Japan (Fig. 5.29, Table 5.4). Migrant groups rapidly reach the higher level of risk of the adopted country, indicating that environmental factors play an important role in etiology. In North America, the trend towards increased incidence is now reversed [1] and a possible beneficial influence of dietary change and/or endoscopic polypectomy has been suggested. In Western Europe, this recent downward trend has not yet been observed. Most cases occur after the age of 60, except in individuals who carry a genetic predisposition.

Etiology

Colorectal cancer most commonly occurs sporadically and is inherited in only 5% of cases. Diet is by far the most important exogenous factor so far identified in the etiology of colorectal cancer [2]. It has been estimated that 70% of colorectal cancers could be prevented by nutritional intervention; various promoting and protective factors have been identified in cohort and case-control studies [3]. There is convincing evidence that a diet high in calories and rich in animal fats, most often as red meat, and

Country	Cumulative incidence (%)	
	Male	Female
Black, USA	5.60	4.22
White, USA	4.98	3.38
Denmark	4.48	3.53
Netherlands	4.25	3.25
Osaka, Japan	4.03	2.28
Qidong China	1.13	0.29
Khon Kaen, Thailand	1.06	0.64

Table 5.4 Cumulative incidence of colorectal cancer. The sum of incidence rates for all ages 0-74 provides a measure of the risk of developing colorectal cancer over a life span, in the absence of any other cause of death.

Fig. 5.30 A diet rich in fresh fruit and vegetables is associated with a lower risk of colorectal cancer.

poor in vegetables and fibre is associated with an increased risk of colorectal cancer. Alcohol intake and smoking (for polyps only) have also been suggested to increase risk. Conversely, a low fat, high vegetable and possibly high fibre diet has a protective effect. Persons with an increased intake of vitamin D and calcium have a reduced risk of colon cancer [4]. Physical activity is also protective. The chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin is associated with a significant risk reduction in certain groups [5] (*Chemoprevention*, p151). It has also been suggested that use of hormone replacement therapy in postmenopausal women may decrease the risk of colon cancer.

Conditions that predispose to the development of colorectal cancer include inflammatory bowel disease and Crohn disease [4]. Patients who have had previous malignant disease are also at a greater risk of developing a second colorectal tumour.

Detection

Bleeding is a common symptom of advanced cancer. Diarrhoea suggests a right-sided tumour and constipation or occlusion suggests a left-sided tumour. However, premalignant lesions (adenomatous polyps) and cancer limited to the mucosa and submucosa are asymptomatic as a rule. Thus screening is now proposed for healthy people, with a view to cancer prevention (*Screening for colorectal cancer,* p163). Appropriate populations for screening may be those at an average risk who are above the age of 50, or individuals selected by a risk factor questionnaire (which may also be used to search for other cases in the family of the person examined). Should the questionnaire findings be positive, the risk is increased 2.5 fold for that individual. The questionnaire is included in the assessment of patients with sporadic colorectal cancer. It also aims to detect genetic syndromes, transmitted in a dominant autosomal fashion, which are much less frequent than sporadic cancer.
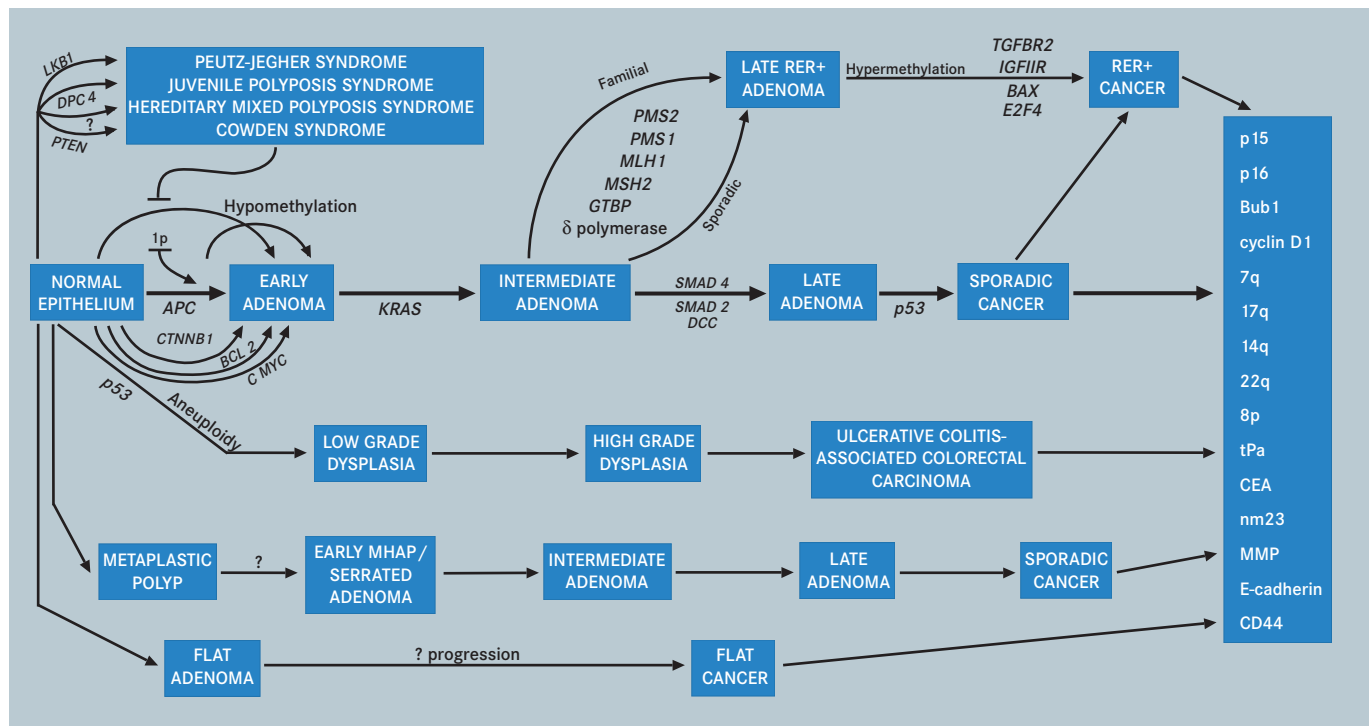

Fig. 5.31 Putative genetic pathways in colorectal cancer. It is thought that the majority of tumours develop according to the original Vogelstein model (bold arrows). See *Multistage carcinogenesis*, p 84. MHAP=Mixed hyperplastic adenomatous polyps.

Diagnostic criteria for hereditary nonpolyposis colorectal cancer
There should be at least three relatives with colorectal cancer:
• One should be a first degree relative of the other two
• At least two successive generations should be affected
• At least one colorectal cancer should be diagnosed before age 50
• Familial adenomatous polyposis should be excluded
• Tumours should be verified by pathological examination

Table 5.5 Criteria for hereditary nonpolyposis colorectal cancer syndrome.

Fig. 5.32 Surgical specimen of the colon from a patient suffering from polyposis coli.
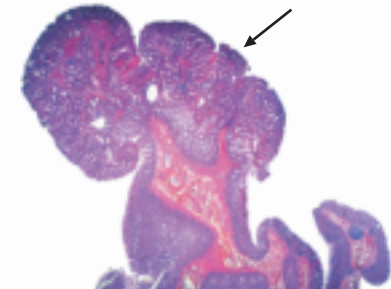

Fig. 5.33 A polypoid tubulovillus adenoma of the colon; the adenomatous proliferation (arrow) forms the head of the polyp, the stalk of which is lined by normal colonic mucosa.
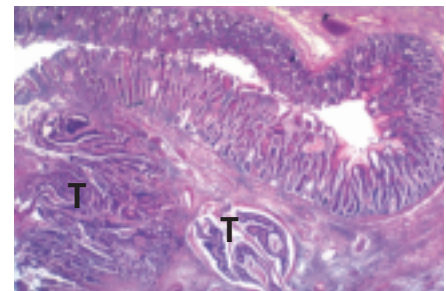

Fig. 5.34 Moderately differentiated adenocarcinoma of the colon (T), infiltrating the submucosa.

The occurrence of colorectal cancer in three successive generations and at a young age in at least one person is among the so-called Amsterdam criteria, which suggest the possibility of hereditary non-polyposis colorectal cancer syndrome, and justifies colorectal exploration and genetic testing (Table 5.5). The detection of diffuse polyposis in the colon (Fig. 5.32) justifies genetic testing for familial adenomatous polyposis syndrome.

Occult bleeding in the stools of asymptomatic persons can be explored by the faecal occult blood test (FOBT). However, this test is reserved for mass screening interventions with assessment of its sensitivity and specificity. In other situations, endoscopy is the gold standard method of detection and should be preferred to the barium enema (Fig. 5.35), which while detecting large tumours is less reliable for the detection of small and flat lesions. Helical CT scan is proposed in most cases as a complementary investigation, helping to assess local tumour invasion and regional and distant metastases. In elderly persons with a poor health status, a colo-scanner with a water enema is a less aggressive procedure than colonoscopy.

A major advantage of endoscopy is the ease with which tissue can be sampled by forceps biopsy and the ability to detect small or flat neoplastic lesions, such as described by the Japanese school and classified as II type (IIa or elevated, IIb or completely flush, IIc or depressed). Detection of such lesions requires a high definition fibroscope with a contrast enhancement system and the use of chromoendoscopy (*Colorectal cancer screen-*

ing, p163). The depressed IIc type is a precursor of advanced cancer. Flexible sigmoidoscopy explores the distal colon; colonoscopy explores the whole of the colon. Another advantage of endoscopy is the potential for interventional procedures and the resection of adenomatous polyps.

Pathology and genetics

Abnormalities of the colonic epithelium, cell atypia and architectural disorders have been classified as premalignant (low-grade and high-grade dysplasia) or malignant (cancer). The current trend is to adopt a classification of tissue samples based upon the term "neoplasia" [6]. The following grades are considered: absence of neoplasia, indeterminate for neoplasia, certain for neoplasia with the two grades of light and severe cell atypia and intra-mucosal cancer. However, there is no invasion of lymph nodes when the lesion is limited to the mucosa. Therefore there is a tendency to use the term "cancer" only when there is a submucosal extension of the lesion. Epithelial abnormalities in polypoid neoplasia are usually called "adenoma" (Fig. 5.33). Only a small fraction of polypoid or flat lesions progress to carcinoma.

The major malignant histological type is adenocarcinoma (Fig. 5.34). Other less common epithelial tumour types include mucinous adenocarcinoma, signet-ring tumours, squamous cell carcinomas, adenosquamous carcinomas and undifferentiated carcinomas.

Genetic susceptibility to colorectal cancer may be attributable to either the polyposis

or the nonpolyposis syndromes. The major polyposis syndrome is familial adenomatous polyposis, caused by a germline mutation in the adenomatous polyposis coli (*APC*) gene. Familial adenomatous polyposis can be associated with nervous system tumours (Turcot syndrome) or with desmoid tumours (Gardner syndrome). The *APC* gene, on chromosome 5q21-22, produces the APC protein, a negative regulator that controls β-catenin concentration and interacts with E-cadherin, a mem-

brane protein involved in cell adhesion. The following genotypic/phenotypic relationships have been demonstrated: *APC* mutations in the first or last third of the gene and attenuated polyposis; mutation after codon 1444 and desmoid tumours; mutations in the central region of the gene and a severe phenotype. Commercial genetic tests involve identification of the mutant *APC* allele by *in vitro* detection of truncated APC protein. Sigmoidoscopy is used to screen gene carriers from the age of 10-12 years.

Hereditary nonpolyposis colorectal cancer (often referred to as HNPCC) syndrome is associated with germline mutations in six DNA mismatch repair genes: *MSH2* and *MSH3*, *MLH1*, *PMS1*, *PMS2*, and *MSH6*. The protein products of these genes correct mismatches that arise during DNA replication (*Carcinogen activation and DNA repair*, p89). Mismatch repair deficiency gives rise to instability in microsatellite DNA and may aid in the diagnosis of this syndrome via the Replication Error positive (RER+) test. Surveillance of female hereditary nonpolyposis colorectal cancer syndrome patients includes exploration of endometrium and ovaries and other potential tumour sites by ultrasound. Kindreds with the Muir-Torre phenotype, as well as a subset of those with Turcot syndrome,

show mutations similar to those observed in classical hereditary nonpolyposis colorectal cancer.

Colon cancer has been the archetype for the correlation of tumour pathology and genetics since the publication of the first such correlative statement by Vogelstein et al. in 1988 (*Multistage carcinogenesis*, p84). As a result of extensive analysis of genetic alterations occurring during tumorigenesis [7-12], understanding of the complex and comprehensive nature of these relationships has since expanded (Fig. 5.31). Sporadic colorectal cancer arises mainly through two distinct pathways. In the first, chromosome instability, the initial mutation is inactivation of the *APC* tumour suppressor gene (*Oncogenes and tumour suppressor genes*, p96) (all tumours) followed by clonal accumulation of alterations in additional oncogenes (*KRAS*, 50% of tumours) and suppressor genes on chromosomes 18 and 17 (*DCC*; *p53* gene, found in 70% of tumours and associated with a shift to a malignant tumour). The second, associated with microsatellite instability, occurs in 15-20% of sporadic colorectal cancers. Alterations have been found to cluster in genes encoding enzymes involved in the repair of DNA mismatches (in particular *MLH1* and *MSH2*).

Histopathology related to poor prognosis includes deep infiltration of the layers of the bowel wall, poor differentiation, high levels of angiogenesis in the tumour and metastasis to numerous or distant lymph nodes. Evidence of host response such as intense inflammatory infiltrate is a favourable prognostic feature. Predictive factors relate to response to therapy [13]. The presence of wildtype *p53* is associated *in vitro* with a good response to many agents. In contrast, mutant *p53* is associated with lack of response to postoperative adjuvant chemotherapy with 5-FU-levamisole. In sporadic colorectal cancer, as well as in hereditary nonpolyposis colorectal cancer syndrome, microsatellite instability is a favourable indicator [12] and the tumour may respond to 5-FU-based chemotherapy. In the future, it is expected that information regarding the molecular biology of the tumour will give
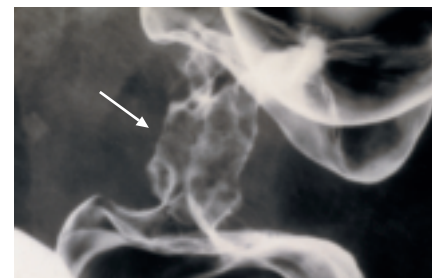

Fig. 5.35 Double contrast barium enema revealing an adenocarcinoma of the colon. Between the proximal (top) and distal (bottom) segment of the colon, the lumen is narrowed with an irregular surface (arrow), due to tumour infiltration.

valuable information regarding prognosis and response to treatment. For example, microarray technology is based on the simultaneous assay showing either deletion or overexpression of multiple gene fragments (around 20,000) and gives a characteristic "fingerprint" of the tumour [14].

Management

The management of familial colorectal cancer requires the systematic genetic and endoscopic screening of the proband (the person presenting with a disorder, whose case serves as a stimulus for a genetic/familial study). Total colo-proctectomy with ileo-anal anastomosis is performed when adenomatous polyps are detected in patients with familial adenomatous polyposis. With hereditary nonpolyposis colorectal cancer syndrome, total colectomy is the treatment for confirmed cancer, with a tendency to prophylactic colectomy in presence of multiple polyps. It has recently been shown that in probands of hereditary nonpolyposis colorectal cancer syndrome families carrying the mutation, surveillance colonoscopy at short (less than two years) intervals is a safe method to detect the first neoplastic lesions and prevents death from cancer.

Precursor adenomatous polyps are usually resected at endoscopy by snare polypectomy, when pedunculated, or by strip resection combined with saline submucosal injection, when sessile or flat. Endoscopic treatment is safe for flat or elevated lesions with intramucosal cancer up to 2 cm in diameter; however this

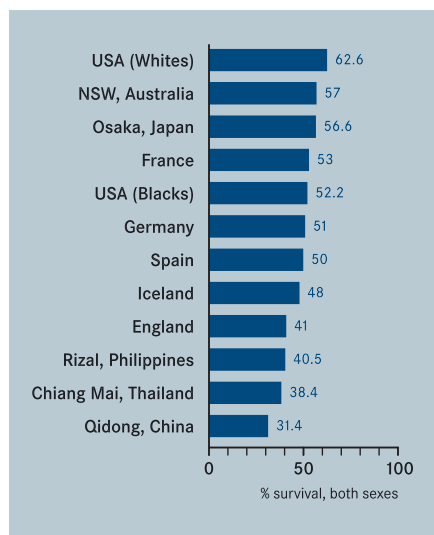|	% survival, both sexes
USA (Whites)	62.6
NSW, Australia	57
Osaka, Japan	56.6
France	53
USA (Blacks)	52.2
Germany	51
Spain	50
Iceland	48
England	41
Rizal, Philippines	40.5
Chiang Mai, Thailand	38.4
Qidong, China	31.4

Fig. 5.36 Five-year relative survival rates after diagnosis of colorectal cancer.

applies to depressed, flat neoplastic lesions (type IIc) only when the diameter does not exceed 1 cm.

Sporadic advanced colonic cancer is treated by segmental colectomy with a tendency to large resection. Adjuvant chemotherapy (5 FU-levamisole or 5 FU-leucovorine) is recommended if lymph node invasion is confirmed and some advocate a similar indication in B2 (sub-serosal) tumours. Recently introduced cytotoxic drugs, such as irinotecan and oxaliplatin, are beginning to become established in treatment regimes [15]. Advanced cancer located in the rectum is treated by neo-adjuvant radiotherapy if the tumour is either T3 (showing local invasion) or N+ (positive lymph nodes). Colorectal cancer is nowadays considered to be a chemosensitive tumour; in some patients, the occurrence of liver or pulmonary metastases does not exclude a curative management based upon combined resection and chemotherapy. The aggressive management of operable patients is based on initial segmental liver or lung resection followed by first line chemotherapy. In inoperable patients, first and second line chemotherapy protocols are proposed and a delayed surgical resection may be considered in some cases. The five-year survival following detection and treatment of colorectal cancer is around 50% (Fig. 5.36).

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WEBSITES

Johns Hopkins Hereditary Colorectal Cancer Website: http://www.hopkins coloncancer.org/subspecialties/heredicolor_cancer/overview.htm

APC gene mutation database: http://perso.curie.fr/Thierry.Soussi/APC.html

LIVER CANCER

SUMMARY

> About 560,000 new cases of liver cancer, usually hepatocellular carcinoma, occur annually, and contribute significantly to cancer mortality worldwide. More than 80% of cases occur in Asia and Africa and irrespective of etiology, the incidence rate is more than twice as high in men as in women.

> In Africa and Asia, hepatocellular carcinoma is most frequently caused by hepatitis B virus infection; concomitant dietary exposure to aflatoxins multiplies the risk. In Japan, this cancer is predominantly caused by hepatitis C virus infection.

> In Western countries, liver cirrhosis due to chronic alcohol abuse is the major etiological factor.

> Hepatocellular carcinoma is almost always lethal, survival from time of diagnosis often being less than six months; only 10% of patients survive five years or more.

Fig. 5.37 Global burden of liver cancer in men. Note the high incidence rates in some African and Asian regions.

Legend: < 3.3 | < 5.6 | < 9.0 | < 15.0 | < 98.9
Age-standardized incidence / 100,000 population

Definition

Hepatocellular carcinoma arises from hepatocytes and accounts for 80% of all primary cancers of the liver. Other tumour types include intrahepatic cholangiocarcinoma (tumours of that part of the bile duct epithelium located within the liver), hepatoblastoma (a malignant embryomal tumour of childhood) and angiosarcoma (arising from blood vessels) and are relatively rare.

Epidemiology

Liver cancer ranks third amongst the organ-specific causes of cancer-related deaths in men worldwide and accounts for almost 4% of all human cancers [1]. Globally, men are three times as likely as women to be afflicted; liver cancer 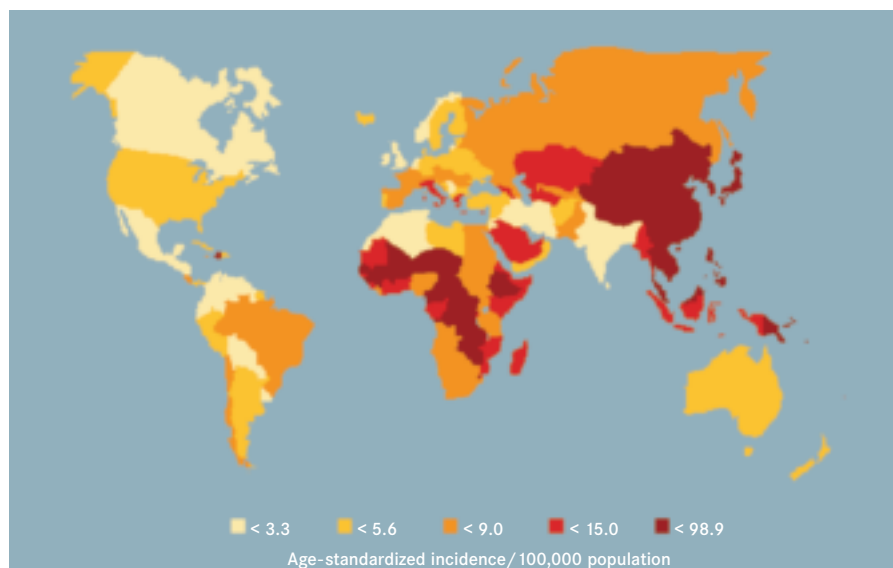is the fifth most common cancer among men worldwide, but is the eighth in women. Liver cancer is a major health problem in developing countries where more than 80% of the world total (457,000 new annual cases) occur. The highest incidence rates are recorded in China (55% of the world total), Japan, South East Asia and sub-Saharan Africa (Fig. 5.37). In both high and low incidence areas, there is great variability in incidence among ethnic groups [2].

Age-specific rates of incidence show marked geographical variation (Fig. 5.38). In the Gambia, age-specific rates peak in the 45-55 years age range, whereas in Europe and the USA, high risk is associated with old age.

Time trends in liver cancer are difficult to interpret due to changes in classification and variable inclusion of metastatic tumours [3]. However, the incidence of hepatocellular carcinoma in Japan, the UK, the USA and several Nordic countries has increased noticeably over the past two decades and has become progressively associated with younger age groups [4]. Mortality rates have increased in several regions, including France. Some of these increases may be the result of improved detection.

Etiology

Experimental evidence in a variety of *in vitro* and animal models has demonstrated the carcinogenic effects of hepatitis B virus (HBV) on hepatocytes through both direct and indirect mechanisms [5]. HBV viral DNA has been found to integrate into hepatocyte DNA and may serve as an insertional mutagen. Viral replication in infected cells and the concurrent host immune response results in persistent inflammation that may eventually progress to cirrhosis and also may dispose toward carcinogenesis; this is the mechanism most commonly exhibited by hepatitis C virus (HCV) (*Chronic infections*, p56). Consistent epidemiological data have associated a significant risk of hepatocellular carcinoma with chronic HBV infection, which accordingly has been categorized as causing cancer in the context of *IARC Monograph* evaluations [6]. Prevalence of carriers in developing coun-

tries is high (10-15%) and it can be estimated that two-thirds of liver cancer cases in developing countries are attributable to this virus [7]. HBV is particularly implicated in hepatocellular carcinoma in Africa and Asia, and HCV in Japan and the USA [4].

In developing countries, dietary ingestion of aflatoxins (produced by the mould *Aspergillus flavus*, which under hot and humid conditions contaminates stored grain), and specifically aflatoxin B_1, is causally associated with development of hepatocellular carcinoma, and exposure to aflatoxins may be synergistic with HBV infection (*Food contaminants*, p43). In developed countries, principal known risk factors are smoking and chronic alcohol abuse. The major clinical hepatocellular carcinoma risk factor is cirrhosis; 70-90% of hepatocellular carcinomas develop in patients with macronodular cirrhosis.

Iron overload caused by untreated haematochromatosis may provoke in some patient series a risk of death of as much as 45% from hepatocellular carcinoma [8]. Hepatocellular carcinoma may occur in 37% of patients with tyrosinaemia who survive to two years old and may occur in patients who have successfully undergone liver transplant. Other metabolic disorders which may carry an increased risk of hepatocellular carcinoma or other liver cancers include alpha-1-trypsin deficiency, hypercitrullinaemia and glycogen storage disease (Table 5.6).

Hepatic cholangiocarcinoma is rare in most populations, the exception being in the population of Northern Thailand where it is associated with chronic infection by the liver fluke *Opisthorchis viverrini*, which is contracted through consumption of infected raw fish.

Detection

Screening programmes by ultrasound examination with or without pre-selection on the basis of raised levels of alpha-fetoprotein have not proved effective in reducing mortality. Recent observations indicate that free DNA originating from tumour cells is detectable in the plasma of liver cancer patients at an early stage. Detection of relevant genetic changes in the plasma (such as *p53* mutation at codon 249 in the inhabitants of high incidence areas and aberrant methylation of *CDKN2A* in most parts of the world) may soon become useful aids in screening tests for hepatocellular carcinoma. The availability of simple, genetic tests would be an important contribution to screening programmes.

Risk factors and predisposing conditions
Hepatocellular carcinoma
Chronic infection with hepatitis B virus
Infection with hepatitis C virus
Chronic liver cirrhosis
Untreated haemochromatosis
Tyrosinaemia
Alcohol abuse
Aflatoxins
Long-term use of oral contraceptives
High dose anabolic steroids
Agents causing peroxisome proliferation
Cholangiocarcinoma
Liver fluke (*Opisthorchis viverrini* and *Clonorchis sinensis*) infection (esp. certain areas of China and South East Asia)
Hepatolithiasis
Thorotrast (no-longer used X-ray contrast medium)
Inflammatory bowel disease
Nitrosamines
Angiosarcoma
Vinyl chloride (polymer industry)

Table 5.6 Risk factors and predisposing conditions for liver cancer.

Common symptoms of hepatocellular carcinoma are abdominal pain, weight loss, fatigue, abdominal swelling and anorexia. Most patients, particularly in sub-Saharan Africa, present with hepatomegaly; other common signs are ascites and jaundice. Hepatocellular carcinoma which infiltrates a cirrhotic liver often compromises the already impaired hepatic function and thus causes death before becoming very large, as is the case in most Japanese and American patients [8]. Intrahepatic cholangiocarcinoma is characterized by general malaise, mild abdominal pain and weight loss, and by jaundice and cholangitis at later stages [9]. The majority of cases can be diagnosed by computed tomography (CT) (Fig. 5.40) and ultrasonography. A definitive diagnosis may depend on histological analysis via fine needle biopsy. Endoscopic retrograde, transhepatic or magnetic resonance cholangiography can identify the level of biliary obstruction in the case of intrahepatic cholangiocarcinoma.
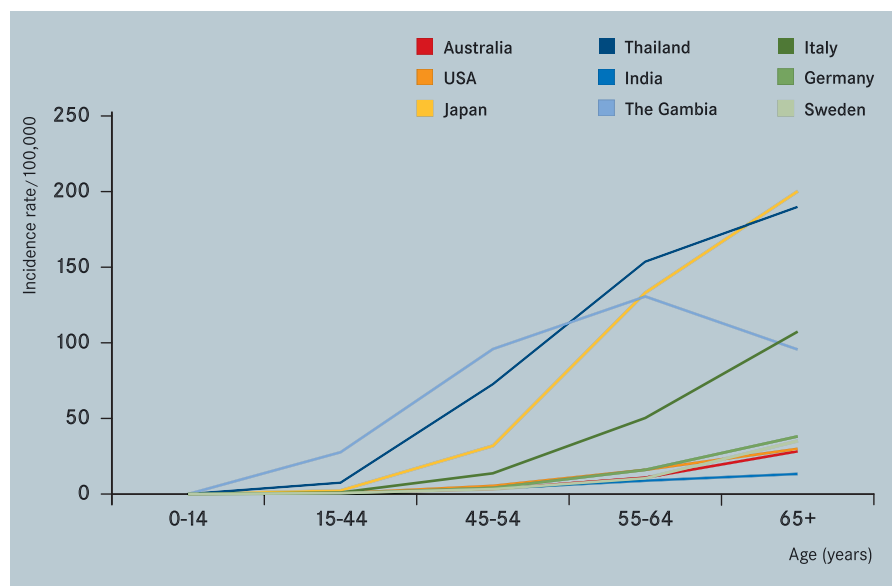

Fig. 5.38 Age-specific incidence of liver cancer in men; rates are higher in young men in areas where viral hepatitis is endemic.

Fig. 5.39 A woman in the Gambia preparing food which is potentially contaminated by aflatoxin. The combination of aflatoxin ingestion and chronic hepatitis B poses a high risk of hepatocellular carcinoma (*Chronic infections,* p56).

Pathology and genetics

Hepatocellular carcinoma is a malignant epithelial tumour derived from hepatocytes, and thus resembles normal liver both structurally and cytologically. Small early-stage hepatocellular carcinomas (<2 cm) are well-differentiated histologically and arranged in a thin trabecular pattern without a capsule (Fig. 5.42) [8]. Tumour cells grow in cords of variable thickness that are separated by sinusoid-like blood spaces. Hepatocellular carcinoma is believed to progress from adenomatous hyperplasia (or dysplastic nodules) through atypical hyperplasia to early hepatocellular carcinoma. Trabeculae become thicker with de-differentiation. Larger cancer nodules may consist of more than two types of tissue of different histological grade [10]. Invasion into the blood vessels, especially the portal vein, is a characteristic of hepatocellular carcinoma. The malignant cells produce alpha-fetoprotein which may be detected in the serum of most patients.

Genetic change in hepatocellular carcinoma may be directly related to relevant environmental factors. In areas with high exposure to aflatoxin B$_1$, mutation of the third nucleotide in codon 249 of *p53* is frequent, compatible with mis-coding due to the binding of aflatoxin (adduct formation) to relevant nucleotides in DNA. There is evidence that mutation of *p53* is an early event in hepatocellular carcinomas in high-incidence areas, whereas it occurs as a late event in progression in industrialized countries. In hepatocellular carcinomas associated with low aflatoxin exposure, mutation of various other sites in *p53* may be detected. Sections of the HBV genome are frequently integrated into tumour DNA and expressed.

Mutational activation of known oncogenes is rare [10]. Point mutations of *KRAS* and co-amplification of the cyclin D1 gene are detected in only a minority of hepatocellular carcinomas. Mutations of the β–catenin gene are evident in about a third of tumours examined. Accordingly, the sequence of genetic events (Table 5.7) that leads to hepatocellular carcinoma is poorly known and may vary from one tumour to another.

Intrahepatic cholangiocarcinoma (Fig. 5.43) comprises cells resembling those of bile ducts, which is the site parasitized by liver flukes [9]. Most intrahepatic cholangiocarcinomas are adenocarcinomas showing tubular and/or papillary structures with a variable fibrous stroma. Mutations of the *KRAS* and *p53* genes are the most common genetic abnormalities identified.

Management

The treatment of primary and malignant liver tumours depends on the extent of the disease and the underlying liver function [11]. The most frequently used staging system is that in which the patient is evaluated according to the adverse criteria of ascites, serum albumin and bilirubin concentration and tumour size. The TNM system (Box: *TNM,* p124) is less useful as it does not take into account underlying liver disease. Liver cancer follows a rapid, progressive course: only about 10% of patients survive at least five years in the
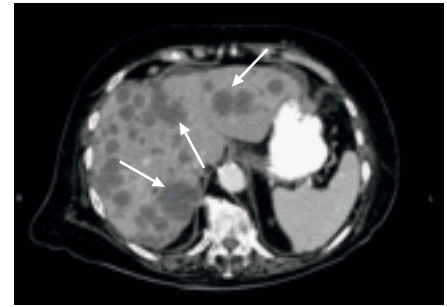

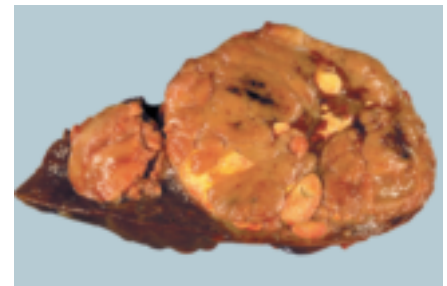Fig. 5.40 CT image of a multifocal hepatocellular carcinoma (arrows).

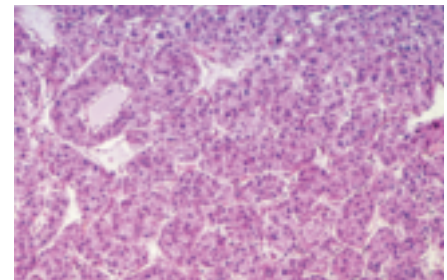Fig. 5.41 Macroscopic appearance of hepatocellular carcinoma.

Fig. 5.42 Histological appearance of hepatocellular carcinoma: a well-differentiated, trabecular carcinoma containing numerous sinusoid-like capillary vessels.
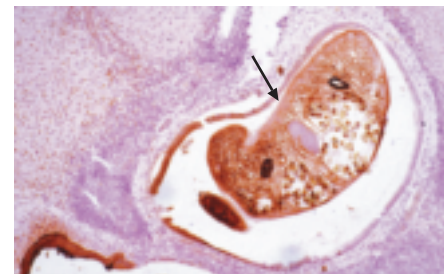

Fig. 5.43 Infection with the liver fluke *Opisthorchis viverrini* (arrow) is typically associated with cholangiocarcinoma in parts of Asia.

USA and the percentage is much lower in developing countries (Fig. 5.44).

In the absence of extrahepatic disease, resection with negative pathologic margins is the mainstay of treatment for malignant liver neoplasms. In patients in whom a small liver remnant is anticipated, portal vein embolization is used to increase the size of the future liver remnant [11]. The fact that most hepatocellular carcinomas occur in a cirrhotic liver excludes many patients from consideration for surgical resection, due to the risk of liver failure. Other techniques used alone or as an adjuvant to resection include radiofrequency ablation and cryoablation. Liver transplantation has been performed in non-resectable patients, although use of this procedure has declined due to a number of factors, including the frequency of death from tumour recurrence, especially in the transplanted liver, and organ shortages.

Hepatocellular carcinoma is largely radiotherapy resistant [10]. Nonsurgical treatments include hepatic artery infusion of drugs or thrombotic agents (port or pump), chemoembolization and percutaneous alcohol or acetic acid injection, although side-effects are many and benefit to the unresectable patient is doubtful [4,11]. Hepatic intra-arterial iodine 131-labelled lipiodol (iodized poppy seed oil) shows promise fo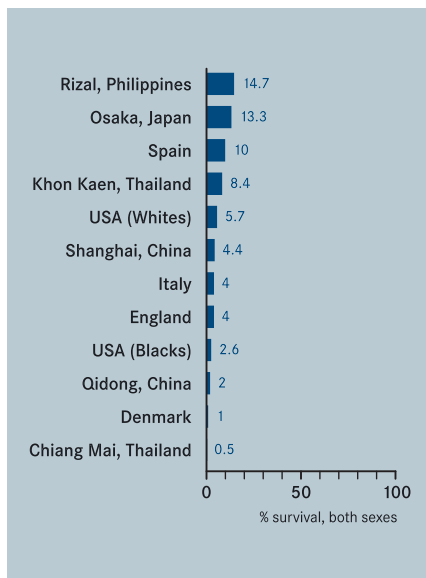r the future [4,12]. Recent results suggest that a chemotherapy regimen combining cisplatin, doxorubicin, interferon and 5-fluorouracil may elicit a response, although previously no agent, either singly or in combination, has been found to improve survival. Hormone therapy is also disappointing, although results with octreotide are more hopeful than with tamoxifen. Metastatic hepatocellular cancer commonly spreads to the lungs and bones. Response to chemotherapy and local regional therapy is poor [12]. The liver is also a frequent site of metastases from cancers at other sites, of which the most common is colorectal cancer.

The poor prognosis and lack of effective therapies for hepatocellular cancer suggest that the development of prevention programmes is of critical importance (*Hepatitis B vaccination*, p144).

Fig. 5.44 Five-year relative survival after diagnosis of liver cancer.

	% survival, both sexes
Rizal, Philippines	14.7
Osaka, Japan	13.3
Spain	10
Khon Kaen, Thailand	8.4
USA (Whites)	5.7
Shanghai, China	4.4
Italy	4
England	4
USA (Blacks)	2.6
Qidong, China	2
Denmark	1
Chiang Mai, Thailand	0.5

Hepatocellular carcinoma
Familial
CDKN 2A, *APC* and *BRCA2*
Sporadic
HBV genome integration
p53
CDKN2A
M6P/IGF2R
SMAD gene family members
Cyclin D and Cyclin A
Altered *MET* function?

Intrahepatic cholangiocarcinoma
KRAS
p53
c-erbB2
MET oncogene
E-cadherin, α-cadherin, β-cadherin
BCL2
Telomerase

Table 5.7 Genes involved in the development of liver cancer.

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WEBSITES

NCI Liver Cancer Homepage:
http://www.cancer.gov/cancer_information/cancer_type/liver/

American Association for the Study of Liver Diseases:
http://www.aasld.org/

CANCERS OF THE MALE REPRODUCTIVE TRACT

SUMMARY

> Prostate cancer accounts for about 200,000 deaths annually worldwide, predominantly afflicting older men in developed countries.

> Risk factors include high caloric intake and low physical activity. Black men have the highest, white men an intermediate, and Asian men a lower risk. Recorded incidence is increasing in many countries, partly as a result of screening for elevated serum levels of prostate-specific antigen.

> Testicular cancer mainly affects young men, with close to 50,000 new cases each year worldwide. Incidence is increasing in many developed countries; its etiology is largely unknown.

> The mean five-year survival rate is higher than 95% mainly due to the efficacy of chemotherapy using cisplatin; long-term disease-free survival can even be achieved in cases of metastatic testicular cancer.

| < 7.6 | < 14.5 | < 23.7 | < 34.7 | < 104.3 |

Age-standardized incidence / 100,000 population

Fig. 5.45 The global incidence of prostate cancer. Rates are highest in developed countries and in some parts of Africa.

PROSTATE CANCER

Definition

The majority of prostate cancers are adenocarcinomas of a heterogeneous nature, which develop primarily in the peripheral zone of the prostate gland.

Epidemiology

Prostate cancer is the third most common cancer in men in the world, with 543,000 new cases each year. In the majority of more developed and developing countries, prostate cancer is the most commonly diagnosed neoplasm affecting men beyond middle age.

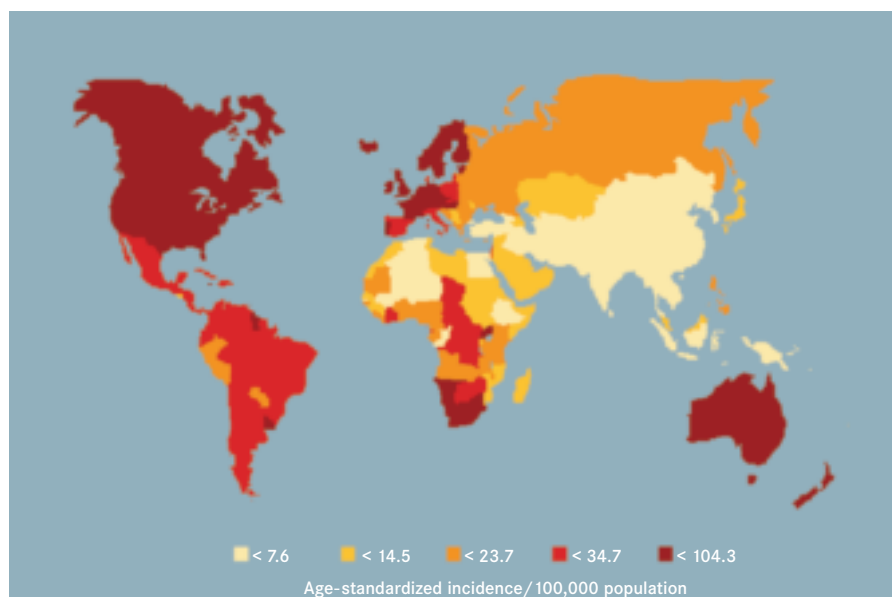In recent times, incidence rates (Fig. 5.45) of prostate cancer have been influenced by the diagnosis of latent cancers (whose presence has been suggested by screening of asymptomatic individuals) and also by detection of latent cancer in tissue removed during prostatectomy operations, or at autopsy. Thus, especially where screening examinations are prevalent, recorded incidence may be very high by comparison with earlier levels. In the USA, for example, the introduction of screening using prostate-specific antigen (PSA) testing has led to an enormous increase in the diagnosis of prostate cancer, recorded incidence now reaching 104 cases per 100,000 population, making it by far the most commonly diagnosed cancer in men (*Screening for prostate cancer*, p160). Similar changes have been observed in Australia, Finland and Sweden. However, incidence rates and, to a lesser extent, mortality rates are rising in many other countries where a possible impact of screening may be excluded. There is even a recognized increase in those Asian countries where risk is low, e.g. in Japan and China, as well as in Africa. Such changes suggest the influence of lifestyle or environmental factors in etiology.

The prevalence of latent prostate cancer shows much less geographic and ethnographic variation than clinical prostate cancer, where the ethnicity-specific rankings are much the same as for incidence [1]. The lifetime risk for microfocal cancer is estimated to be at least 30% of the male population, with progression to clinical cancer occurring in about 10%, while the lifetime risk of dying from prostate cancer is approximately 3%.

Incidence and mortality increase with ageing, with peaks somewhere within the seventh decade, depending on the degree of awareness and the establishment of population screening programmes in different populations. The low fatality rate means that many men are alive following a diagnosis of prostate cancer – an estimated 1.37 million at five years in 2000 - making this the most prevalent form of cancer in men. More than any other, this is a cancer of the elderly. Thus, about three-quarters of cases worldwide occur in men aged 65 or above.

Certain	Possible	Uncertain
Age	Androgens	Body size
High fat diet	Race	Sexual activity
Family history	*Estrogens*	Vasectomy
	Selenium	*Vitamin A*
	Vitamin E/D	*Calcium*
	Phyto-estrogens	*Lycopene*

Table 5.8 Risk and protective (in italics) factors for prostate cancer.

The distribution of mortality rates is less affected than incidence by the effects of early diagnosis of asymptomatic cancers (whether through screening, or by detection of latent cancer in tissue removed during prostatectomy operations). Mortality rates are comparatively high in North America, Northern and Western Europe, Australia/New Zealand, parts of South America (Brazil) and the Caribbean, and in much of sub-Saharan Africa and low in Asian populations, and in North Africa (Fig. 5.46). The difference in mortality between China and the USA is 26-fold (while it is almost 90-fold for incidence). Racially based differences are evident within the United States, where the black population has the highest incidence (and mortality) rates, those rates being some 35% higher than in whites, who in turn have rates considerably higher than populations of Asian origin (Chinese, Japanese, Korean).

Etiology

Age is the strongest risk factor for prostate cancer. Development of this malignancy is a multi-step process associated with a long natural history [2]. It can be inferred that the initiation of preneoplastic lesions and microscopic cancer is influenced by environmental factors which, in turn, implies a case for lifestyle causes and primary prevention.

Although many of the risk factors for adenocarcinoma of the prostate (Table 5.8) are weakly linked, the strong association of race, familial and geographic patterns with mortality directs attention to a significant role for genetic-environmental interactions as determining patterns of disease. Dietary patterns suggest that saturated fat is a significant risk factor, while micronutrients such as the vitamins A, E and D, selenium, lycopene and calcium may exercise a protective effect against cancer.

The role of hormones, especially androgens, is obviously important, granted the impact of orchidectomy (excision of the testes) on progression. However, an endocrine basis for carcinogenesis is still not well understood. Genetic polymorphisms in the androgen receptor may be more important than any imbalance of hormones in the circulation. Studies of body size, vasectomy, sexual activity and cigarette smoking as risk factors have produced inconclusive, equivocal results.

A diet characteristic of Asian countries such as Japan and China, essentially a low fat intake with consequent low body weight, with an intake of relatively high levels of phyto-estrogens (Box: *Phyto-estrogens*, p78) may provide the means of restraining the growth and progression of prostate cancer. A strategy for prevention would be to increase the intake of phyto-estrogens, essentially isoflavonoids, lignans and possibly certain flavonoids [3]. The years of potential life saved by preventive measures for prostate cancer may be less than for cancers occurring earlier in life, but the number of men with the disease worldwide adequately justifies a focus on this effort (*Screening for prostate cancer*, p160).
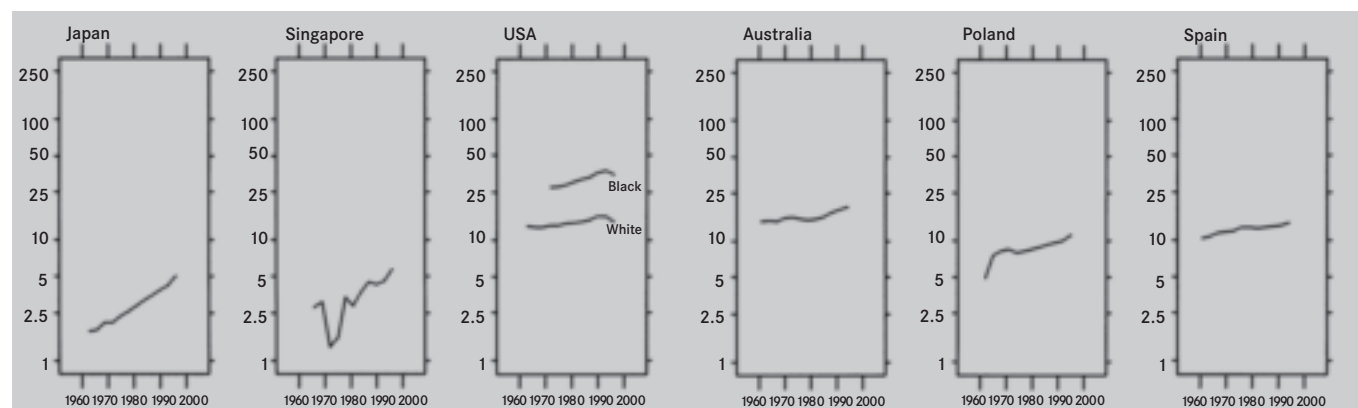

Fig. 5.46 Trends in prostate cancer mortality. Although mortality rates increased generally in the last 30 years, in some places, e.g. the USA, mortality is now falling. D.M. Parkin et al. (2001) *Eur J Cancer*, 37 Suppl.8: S4-66.
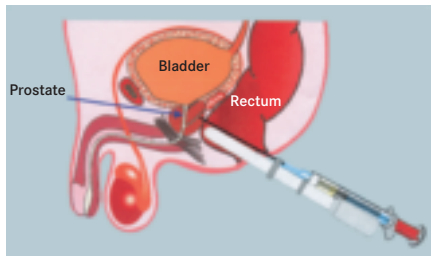
Fig. 5.47 Diagram describing patient configuration during transrectal ultrasound imaging of the prostate gland, which is an important technique used to measure prostate volume and to direct biopsies in prostatic tissue.
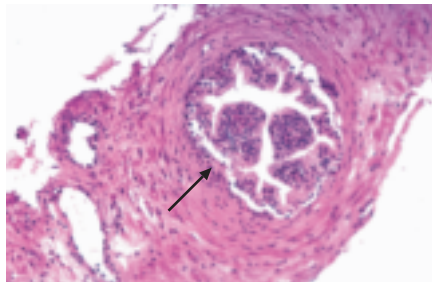

Fig. 5.50 Stages of prostate cancer progression are correlated with loss of specific chromosome regions and of candidate tumour suppressor genes.

Fig. 5.48 A premalignant lesion of the prostate gland: this biopsy shows prostatic intraepithelial neoplasia (arrow) within a dilated gland.
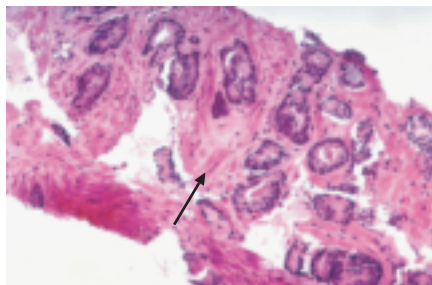
Fig. 5.49 A biopsy from the prostate gland showing a focus (arrow) of moderately differentiated adenocarcinoma with tubular architecture.

Detection

The presence of lower urinary tract symptoms (e.g. difficulty in urinating, frequent need) above age 50 are mostly due to concomitant benign prostatic hypertrophy. Latent cancer can progress to adenocarcinomas, which can infiltrate local urogenital organs and give rise to distant metastases, particularly to the bones. Digital rectal examination is the simplest way to d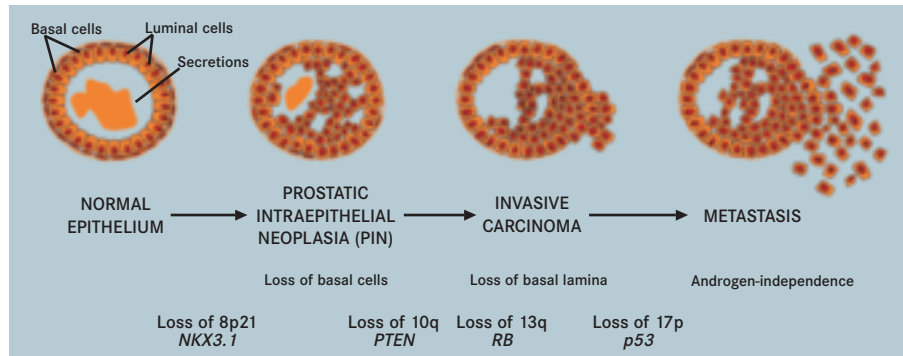etect anatomical abnormalities of the prostate gland, and asymmetry and induration are indicative of prostate cancer. Raised levels of PSA may confirm the suspicion and mandate an ultrasound-guided biopsy, after the patient has been informed of the consequences of both medical procedures [4]. Good clinical practice requires that symptomatic patients need a differential diagnosis (analysis of clinical data to determine specific nature of disease) whereas asymptomatic patients, especially those over 70 years of age, must be counselled as to the benefits and disadvantages of further investigation and treatment. Imaging provides no further support to confirm the suspicion of prostate cancer. Transrectal ultrasound guided biopsies establish the dimensions of the prostate gland and enable effective location of the usual six core biopsies (Fig. 5.47). Radiological examinations such as CT scans, MRI and especially bone scans, are performed only in order to stage a diagnosed cancer. Radiolabelled immunoproteins may well offer a potential imaging improvement.

Pathology and genetics

Cancer of the prostate is a slow but continuously growing form of neoplasia that is present in its preclinical form in men from the age of 30, remaining latent for up to 20 years before progressing to the aggressive, malignant clinical cancer that generally attains its peak incidence in the seventh decade. Prostatic intraepithelial neoplasia (Fig. 5.48) is thought to represent the precursor of prostate cancer. Microfocal, latent or incidental prostate cancer are terms used to describe small histological tumours found at autopsy, or in surgical specimens, the prevalence of which is correlated with age. The studies of Sakr [5] directed attention to the relatively high incidence of these microscopic cancers before the age of 50.

Most instances of prostate cancer are adenocarcinomas (Fig. 5.49), generally heterogeneous, that develop primarily in the peripheral zone of the prostate gland. A clinical cancer is recognized as having a volume over 0.5 cm^3 and is less well differentiated than the latent cancers. Slow growth with long doubling times, as well as de-differentiation over time, even in the advanced stages of the disease, are the hallmarks of prostate cancer [3]. The stages of progression are associated with specific genetic alterations.

It is estimated that up to 10% of all cases of prostate cancer may be inherited. Two familial genetic susceptibility loci have thus far been mapped to the X chromosome and to chromosome 1p [6]. Prostate cancer is genetically unstable and its genomic mutations can be divided into five major types: subtle sequence changes, alterations in chromosome number (aneuploidy), chromosome translocations, gene amplifications and allelic deletions. Tumour growth suppressor proteins such as p53 and bcl-2 are currently being evaluated as prognostic factors, together with an associated wide array of other genetic alterations [7-9].

Management

The dramatic division between localized curable prostate cancer versus the advanced incurable disease has provoked heated controversies regarding the impact of early diagnosis and appropriate management. For localized disease in patients with a reasonable life expectancy, cure is the ultimate goal [10]. Radical prostatectomy (retropubic, perineal or laparoscopic) is usually recommended for patients with a life expectancy of greater than ten years. Although the cure rate is very high, side effects may include incontinence (2-10%) and impotence (30-90%). Due to subsequent incapacity to produce semen, men who wish to father children may be advised concerning sperm-banking or retrieval. Radiotherapy is effective and may be recommended for patients who are not suitable for surgery. Proctitis (inflammation of the rectum) is, however, a common side effect of conventional external beam therapy (occurring severely in 3-5% of patients), as is erectile dysfunction (6-84%) [11]. Alternatives include conformal radiotherapy or brachytherapy. Locally advanced disease is frequently managed by a combination of endocrine therapy and radiotherapy, while endocrine treatment is the mainstay for metastatic disease. Such endocrine treatment may comprise luteinizing hormone-releasing hormone agonists, anti-androgens or orchidectomy. The initial choice of treatment is best done after counselling the patient and with access to a multidisciplinary team. Endocrine treatment almost invariably achieves a remission of the disease for a period, followed by a relapse and the development of endocrine unresponsive cancer. This type of disease needs aggressive but compassionate management, depending upon the general health status of the patient. More research is, however, essential to establish specific optimal treatment for the individual patient.

Stage and grade determine the outcome of the disease in both localized and advanced disease. The limiting factor to cure is the presence of extraprostatic extension of the disease, a frequent companion to surgical treatment due to the uncertainty of detecting extracapsular perforation before the operation. The TNM staging system (Box: *TNM*, p 124) is universally recognized. The differentiation or grade of the tumour is a well-recognized dominant prognostic factor that predicts the outcome of disease in all stages and independently of the applied therapy. The Gleason grade scoring system is now widely accepted as a means to assess the histological degree of differentiation. Serum PSA values and tumour size are valuable indicators; other promising potential prognostic factors include kallikreins, microvessel density, epidermal growth factors and androgen receptors. Tuning or integrating the different prognostic factors into a nomogram, or an analysis by artificial neural net system may provide better probabilities for the individual patient in the future [12].

Survival time after diagnosis is significantly longer in high-risk countries (80% in the USA compared to 40% in developing countries), although this more favourable prognosis could well be due to the greater numbers of latent cancers being detected by screening procedures in these countries.

CANCER OF THE TESTIS

Definition

The most common malignant tumours of the testis (>90%) are germ cell tumours, which are classified as seminoma or nonseminoma. Less common testicular tumours are Leydig cell tumours, Sertoli tumours, rhabdomyosarcoma and, in the elderly, non-Hodgkin lymphoma.

Epidemiology

Cancer of the testis accounts for 1.5 % of all male cancers in most markedly affected populations and about 0.5% elsewhere. About 49,300 new cases are diagnosed each year. A rapid increase in incidence has been observed in most countries, such that in some populations testicular cancer is the most common malignancy among young men at age 15-34. The reasons for this trend are not well understood, although improved diagnostic procedures may be partially responsible. The highest incidence is in Central Europe (Denmark, Norway and Germany) and generally in Caucasian populations of developed countries (Fig. 5.51). In the USA and Western Europe, the lifetime incidence of germ cell tumours is one in 500 or 15-20 per 100,000 males per annum. Incidence is low in Africa and Asia, including Japan, with only Israel having an intermediate rate.

Cancer of the testis can occur at all ages, risk being maximal during the third and fourth decades of life and declining after age 50; the median age at diagnosis for testicular nonseminoma is 24 years and a
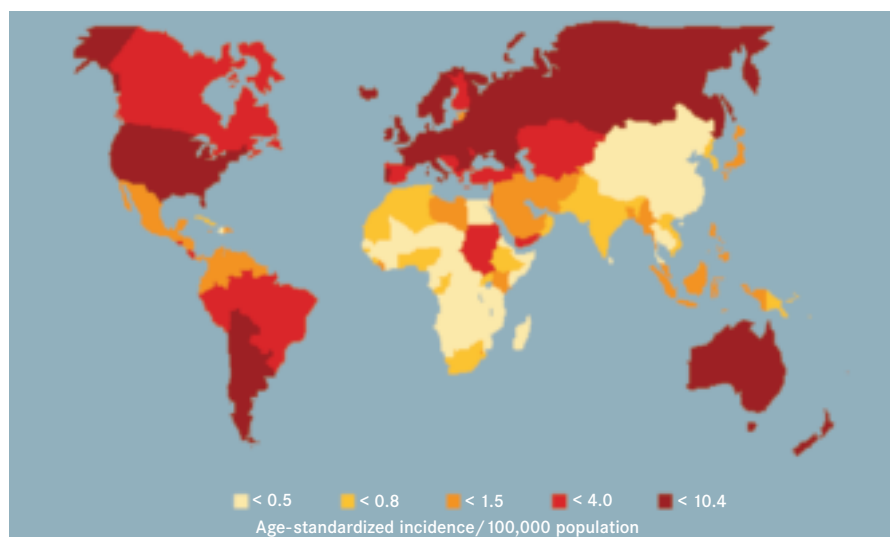

Fig. 5.51 Global incidence of testicular cancer. The highest rates are in affluent Caucasian populations.
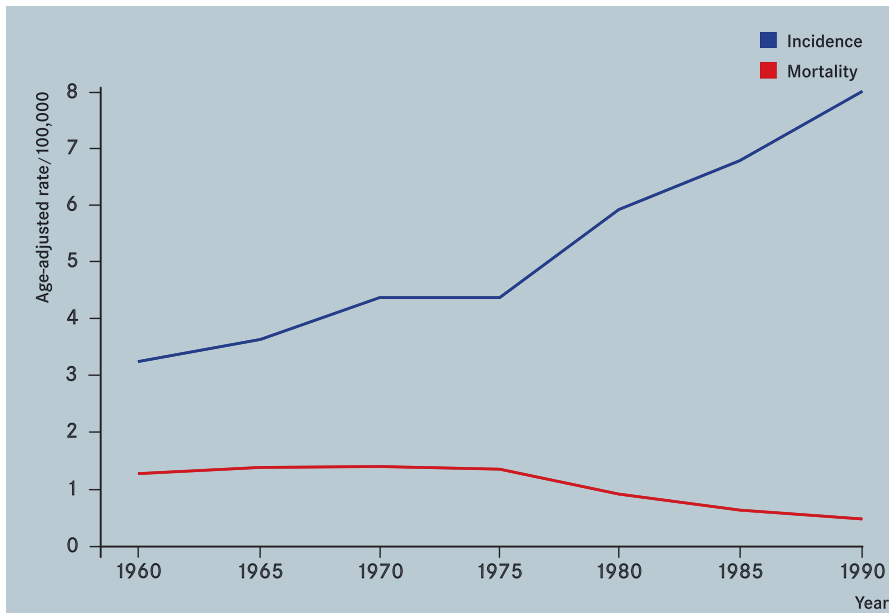
Fig. 5.52 Trends in incidence and mortality of testicular cancer in Norway, 1960-1990. Incidence has increased significantly while mortality has decreased, due to effective chemotherapy.
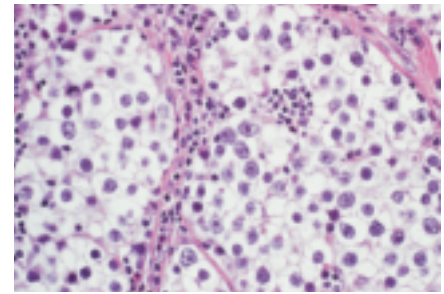

Fig. 5.53 Histology of a seminoma with uniform cells resembling primitive germ cells, large vesicular nuclei and a glycogen-rich clear cytoplasm. Note the scattered lymphocytic infiltrates.
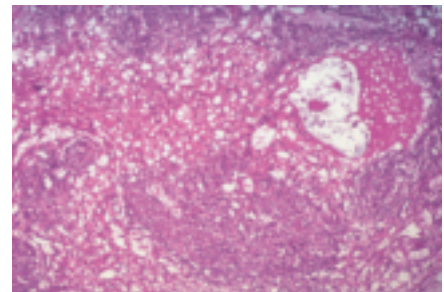

Fig. 5.54 Embryonal carcinoma consisting of a pleiomorphic proliferation containing glandular structures.

decade older for testicular seminoma. Mortality has declined markedly since the introduction of cisplatin as the basis of chemotherapy in the mid-1970s.

Etiology
Generally relevant environmental causes of testicular cancer have not been established. There is an increased incidence of the disease in individuals with a history of an undescended testicle, testicular feminization and those with a family history of testicular cancer. *In utero* exposure to exogenous estrogens may increase the risk of testicular cancer as a result of increased incidence of cryptorchidism and dysgenesis. A history of maternal exposure to diethylstilbestrol has been associated with an increased relative risk of up to 5.3 [13]. Testicular cancer is more common in higher socioeconomic groups. Hormonal and genetic factors seem likely to play an important, but currently unclear, role as risk factors; other factors may include the influence of heat [14].

Detection
Most patients with testicular germ cell tumours present with a painless swelling or a nodule in the testis. Other common presentations include back pain, (caused by retroperitoneal metastasis), haemoptysis (consequent upon pulmonary metastases) and gynecomastia (excessive development of male mammary glands). Diagnosis is based on physical examination, ultrasonography and biopsy. In patients with nonseminoma, serum tumour markers alpha-fetoprotein and/or human chorionic gonadotrophin are elevated in 80% of patients with disseminated disease and in 50% of patients with early stage disease. Patients with testicular seminoma may have modestly elevated levels of human chorionic gonadotrophin and of lactic dehydrogenase.

There are no reliable screening tests for testicular cancer. Due to low incidence and a high cure rate, advocacy of testicular self-examination and the impact of self-assessment are controversial.

Pathology and genetics
About 90% of testicular malignancies arise from germ cells and these tumours are classified as seminoma (40%) (Fig. 5.53) or nonseminoma, which includes embryonal tumours (20-25%) (Fig. 5.54), teratoma (25-30%) and choriocarcinoma (1%). Germ cell tumours can also arise from extra-gonadal primary sites. Ovarian germ cell tumours of young women share clinical features and treatment approaches with male germ cell tumours. All germ cell tumours are commonly associated with the presence of isochromosome 12p (an abnormal chromosome 12 with two identical short arms), a region which contains the gene for cyclin D2 [15]. The initiation of a germ cell tumour is associated with various aberrations in the normal developmental pathway of the germ cell (Fig. 5.55).

Management
Current management of germ cell tumours should yield average cure rates in excess of 95%, and even 80% of patients with metastatic disease respond to chemotherapy, radiotherapy and surgery (Fig. 5.56). However, survival in develop-
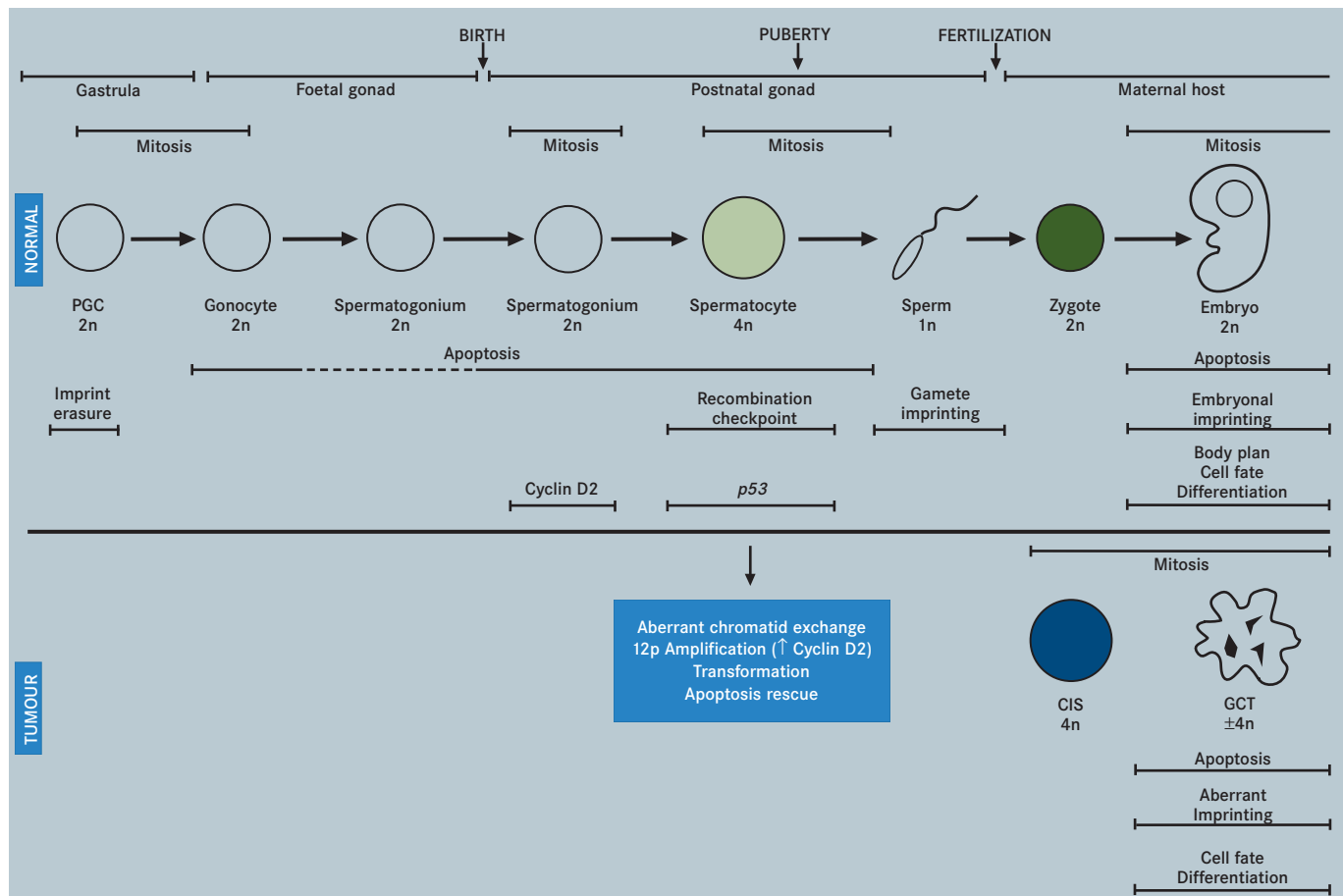
Fig. 5.55 Normal and neoplastic male germ cell development. The division of a precursor cell, the spermatocyte (4n), produces 4 sperm cells each with one set of chromosomes (1n). The fusion of egg and sperm to form the zygote doubles the number of chromosomes to the normal complement (2n). Aberrant development may produce a cell which has twice the normal chromosomal complement (4n). CIS = carcinoma *in situ,* GCT = germ cell tumour, PGC = primordial germ cell.

ing countries is only 42% to 61%, an indication of limited access to appropriate therapy [13].

Seminoma
Stage I disease, confined to the testis, is managed by post-operative radiotherapy to the retroperitoneal nodes which reduces risk of recurrence from about 20% to 2%. Patients who relapse either during surveillance or after radiation are reliably cured with chemotherapy or radiation at the time of relapse. Normal levels of alpha-fetoprotein, the presence of any human chorionic gonadotrophin or any lactic dehydrogenase are good prognostic factors. Patients with abdominal involve-ment from seminoma should receive either radiation therapy (<5 cm bulk disease) or primary chemotherapy (>5 cm bulk disease).

Nonseminoma
Patients with local nonseminoma confined to the testis should be offered either aggressive surveillance or nerve-sparing retroperitoneal lymph node dissection. Surveillance requires monthly chest X-rays and assay of markers and two-monthly abdominal CT scans for one year. In the second year following diagnosis, chest X-ray and assay of tumour markers should be carried out every six months and CT performed every three months. Good prognostic factors include low levels of alpha-fetoprotein (<1000 ng/ml), human chorionic gonadotrophin (<5000 iu/L) and lactic dehydrogenase (<1.5 times the upper limit of normal). Approximately 30% of patients under surveillance will relapse and are reliably cured with chemotherapy. Retroperitoneal lymph node dissection is both diagnostic and therapeutic. It also eliminates the need for abdominal imaging in follow-up.

Patients with abdominal involvement of nonseminoma should receive retroperitoneal lymph node dissection (<2 cm disease) or primary chemotherapy (>2 cm disease). Those who undergo retroperitoneal lymph node dissection and are
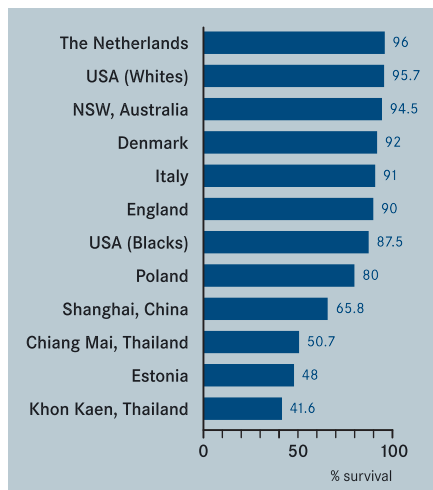
	% survival
The Netherlands	96
USA (Whites)	95.7
NSW, Australia	94.5
Denmark	92
Italy	91
England	90
USA (Blacks)	87.5
Poland	80
Shanghai, China	65.8
Chiang Mai, Thailand	50.7
Estonia	48
Khon Kaen, Thailand	41.6

Fig. 5.56 Five-year relative survival rates after diagnosis of testicular cancer.

found to have positive nodes can consider two cycles of adjuvant chemotherapy (100% cure rate).

Disseminated germ cell tumours
Guidelines for treatment of disseminated germ cell tumours (both seminoma and nonseminoma) are driven by the International Germ Cell Consensus (IGCC) prognostic index. Patients with low-risk nonseminoma (56% of cases) or seminoma (90% of cases) should receive three cycles of bleomycin, etoposide and cisplatin (BEP). Cure rate is approximately 90-95%. Patients with intermediate-risk disease or high-risk disease should receive four cycles of BEP, with an expected cure rate of 75% or 50% of patients respectively.

Patients with nonseminoma who have normalized serum tumour markers and residual radiographic abnormalities should be considered for post-chemotherapy resection of residual disease. Teratoma (a malignant tumour that contains a variety of embryo-derived tissues, such as bone, muscle, cartilage, nerve, tooth buds) and persistent cancer are common findings in this setting. In contrast, patients with seminoma and residual masses after chemotherapy should be simply observed, as teratoma and residual cancer are not common findings in this situation.
Patients with recurrent disease after chemotherapy still have the potential for cure. Salvage chemotherapy with vinblastine, ifosamide and cisplatin cures approximately 25% of these patients.

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WEBSITES

Information for GPs: Screening for Prostate Cancer: http://www.sesahs.nsw.gov.au/publichealth/Cancer Control/default.htm

The Prostate Cancer Research Institute (USA): http://www.prostate-cancer.org/

NCI Prostate Cancer Homepage : http ://www.cancer.gov/prostate

CANCERS OF THE FEMALE REPRODUCTIVE TRACT

SUMMARY

> Cervical cancer is the second most common cancer of women worldwide with more than 470,000 new cases per year. Of about 230,000 deaths every year, more than 80% occur in developing countries. Five-year survival rates are up to 70%.

> Sexually transmitted infection with human papillomavirus is fundamental to development of carcinoma of the cervix.

> Population-based screening has greatly reduced mortality in developed countries

> Endometrial cancer mainly affects postmenopausal women in developed countries; 188,000 new cases are diagnosed annually and obesity is a major risk factor.

> About 190,000 cases of ovarian cancer occur each year, predominantly among postmenopausal women in developed countries; five-year survival rates are about 40%.

Legend: < 9.3   < 16.1   < 23.8   < 35.8   < 93.9
Age-standardized incidence / 100,000 population
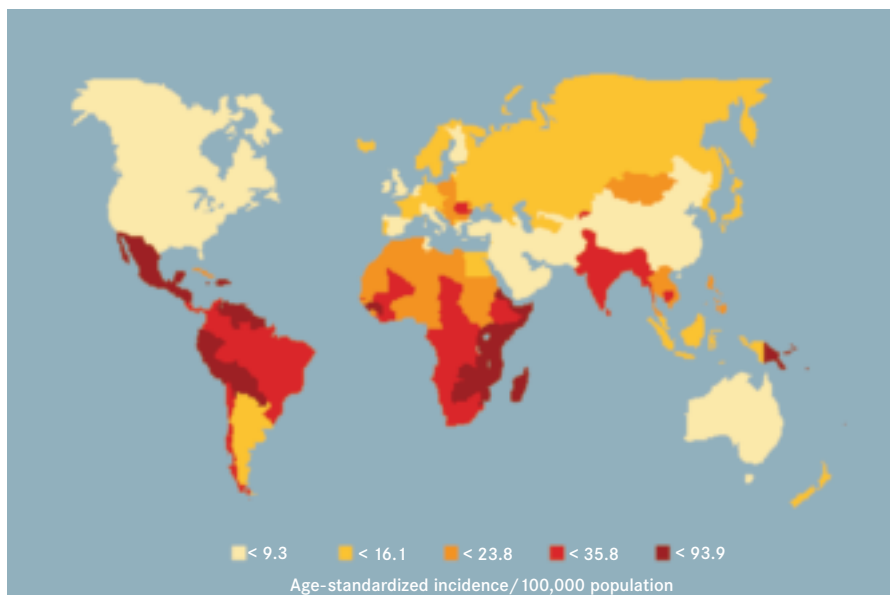
Fig. 5.57 The global burden of cervical cancer. Note the high incidence rates in Central and South America, Southern Africa and India. Today, more than 80% of all cervical cancers occur in developing countries.

CERVICAL CANCER

Definition

The majority of epithelial tumours of the cervix are squamous cell carcinomas (85%). Adenocarcinomas are less common. Most cervical carcinomas arise at the junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix, a site of continuous metaplastic change, especially *in utero,* at puberty and during a first pregnancy.

Epidemiology

Cancer of the cervix is the second most common cancer among women worldwide, second only to breast cancer; about 470,000 new cases are diagnosed each year. 80% of cases of cervical cancer occur in developing countries where, in many regions, it is the most common cancer of women. The highest incidence rates are in South America and the Caribbean, sub-Saharan Africa, and South and South-Eastern Asia (Fig. 5.57). However, very low rates are observed in China, and in Western Asia. In developed countries, the incidence rates are generally low, with age-standardized rates of less than 15 per 100,000, with the exception of Eastern Europe, where incidence rates range from 18-35 per 100,000. The incidence of cancer of the cervix begins to rise at ages 20-29, and then increases rapidly to reach a peak at around ages 45-49 in European populations, but often rather later in developing countries.

Incidence and mortality have declined markedly in the last 40 years in Western Europe, USA, Canada, Australia and New Zealand, mainly in relation to extensive screening programmes based on exfoliative cervical cytology, typically by means of the Pap smear (*Screening for cervical cancer,* p167). Nevertheless, in several countries, notably the UK, Australia, New Zealand, and in central Europe, there have been increases in risk in younger women, probably the result of changes in exposure to risk factors. These changes are most evident for adenocarcinomas, which share to some extent the etiological agents of squamous cell carcinomas, but for which cytological screening is ineffective in countering the increase in risk. In developing countries the situation is more mixed, with high rates persisting in some areas (Latin America, India, Africa), and declines elsewhere, most notably in China.

Etiology

Molecular epidemiological studies have shown that certain human papillomavirus types (HPV) are the central cause of cervical cancer and cervical intraepithelial neoplasia (CIN) [1, 2, 3]. It is now clear that the well-established risk factors associat-

Fig. 5.58 A "Healthy Women" group in a Nigerian village discusses the benefits of condom usage to prevent sexually transmitted diseases.
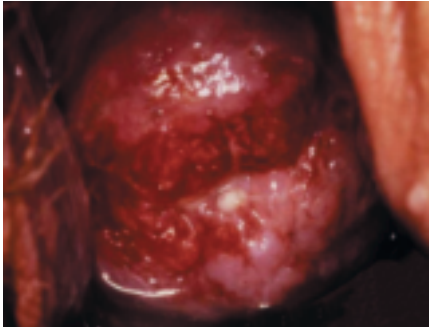

Fig. 5.59 An invasive cancer of the cervix, seen by unaided visual inspection.

Phylogenetic Classification	Epidemiologic Classification	
	High risk	**Low risk**
High risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82, 26, *53, *66*	70
Low risk	73	6, 11, 40, 42, 43, 44, 54, 61, 72, 81, CP6108
* **The epidemiologic classification of these types as probable high-risk types is based on zero controls and one to three positive cases.**		

Table. 5.2 B. Phylogenetic and Epidemiologic Classification of HPV Types. Munoz et al. *N Engl J Med* 348:518-527 (2003).

ed with sexual behaviour, such as multiple sexual partners and early age at initiation of sexual activity, simply reflect the probability of being infected with HPV. HPV DNA has been detected in virtually all cervical cancer specimens [4, 5]. The association of HPV with cervical cancer is equally strong for the two main histological types: squamous cell carcinoma and adenocarcinoma. Over 100 HPV types have been identified and about 40 can infect the genital tract (Table 5.2 B). Fifteen of these have been classified as high-risk (HPV 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), three as probably high-risk (HPV 26, 53, and 66) and twelve as low-risk (HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108) [1, 4, 6]. However, since only a small fraction of HPV-infected women will eventually develop cervical cancer, there must be other exogenous or endogenous factors which, acting in conjunction with HPV, influence the progression from cervical infection to cervical cancer. The assessment of the role of these co-factors requires that the central and strong effect of HPV is taken into account. A review of studies fulfilling this requirement has revealed that high parity, smoking and long-term use of oral contraceptives are co-factors that increase the risk of cervical cancer. The role of additional co-factors such as, herpes simplex virus type 2 (HSV-2), Chlamydia trachomatis infection, HIV and other causes of immunosuppression, certain nutritional deficiencies and genetic susceptibility, is being investigated.

Detection

Early changes in the cervix, specifically cervical intraepithelial neoplasia, can be detected years before invasive cancer develops, and this is the basis for the effectiveness of cytological screening in secondary prevention. The diagnosis of cervical cancer is made on examination of cytological samples taken from the endocervix with a cytobrush and from the ectocervix with an Ayre's spatula (an ectocervical or a Papanicolaou smear) [7]. A tissue specimen may also be obtained by colposcopy and biopsy, which may be the loop electrosurgical excision procedure. In the course of screening, false negatives are common so all suspicious lesions are biopsied. If clinical cancer is apparent, a punch biopsy specimen is evaluated. Patients with abnormal Pap smear and no visible lesion require colposcopy and biopsy. The diagnosis of microinvasive carcinoma is made from cone biopsy or hysterectomy specimen pathology.

Cervical cancer does not tend to produce any symptoms in the early stages. Only when invasive disease is established do symptoms such as vaginal bleeding, discharge and pain become manifest.
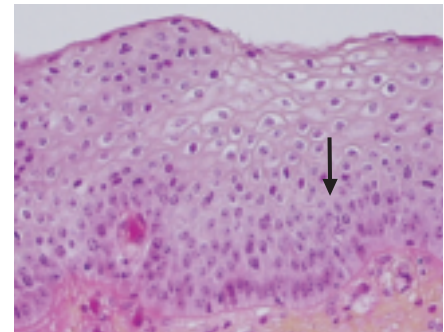

Fig. 5.60 Histology of cervical intraepithelial neoplasia stage I (CIN 1). Note that dysplastic cells (arrow) are confined to the lower third of the epithelium.
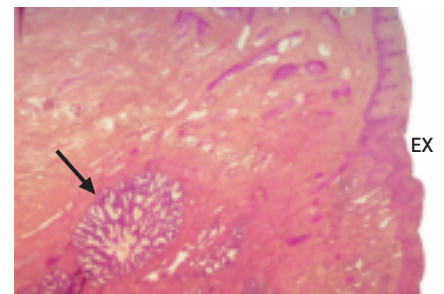

Fig. 5.61 A well-differentiated mucinous adenocarcinoma (arrow) with a papillary architecture developing from the endocervical mucosa, deep under the normal squamous epithelium of the exocervical mucosa (EX).
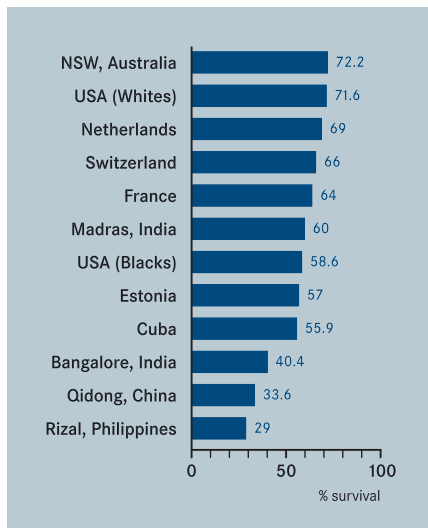
Fig. 5.62 Five-year relative survival rates after diagnosis of cervical cancer.

Advanced carcinoma is suggested by back-pain, oedema of the lower extremity, a non-functioning kidney (due to ureteral obstruction), invasion of sacral nerve branches or extranodal extension and encroachment of the pelvic wall veins and lymphatics [6].

In the event of invasive disease, investigations are undertaken to determine whether metastatic disease is present, i.e. chest radiography, blood cell count and serum chemistry. Intravenous pyelography is used to investigate the possibility of uretic obstruction; abdominal CT and MRI are used to indicate spread and to take tumour measurements, respectively. Cytoscopy and sigmoidoscopy are necessary in the event of anterior or posterior spread.

Pathology and genetics

Precursor lesions of the cervix are commonly classified using terminology for histological diagnosis, thus mild dysplasia is categorized as cervical intraepithelial neoplasia CIN I, moderate dysplasia is CIN II, and severe dysplasia, CIN III. However, newer terminology for precursor lesions of the cervix classifies them as squamous intraepithelial lesions, which are graded from low (mild dysplasia, usually diploid or polyploid, associated with various HPV types) to high (associated with intermediate or high-risk HPV type, typically aneu-

ploid, moderate or severe dysplasia or carcinoma *in situ*) [6]. One of the precursors of invasive adenocarcinoma is recognized as adenocarcinoma *in situ*. This is sometimes difficult to diagnose, often not being detected by Pap smear [8].

Squamous cell carcinomas may be either large cell non-keratinizing or large cell keratinizing, or a less common variant, such as the well-differentiated verrucous carcinoma. The worldwide prevalence of adenocarcinomas of the cervix has increased from 5% in 1950-60 to 20-25% of all cervical tumours [6]. The most common type is mucinous adenocarcinoma, which may be intestinal, endocervical or signet-ring, followed by endometrioid adenocarcinoma. Another epithelial tumour type consists of a mixture of squamous cell carcinomas and adenocarcinomas.

Subsequent to infection, the HPV genome of high-risk types becomes stably integrated into the host DNA, commonly near cellular oncogenes such as *C-MYC* and *N-MYC*, or into regulatory sequences, such as the genes encoding transcription factors Erg and Ets-2 [9]. The observation that low frequencies of *p53* gene mutations are found in tumours associated with HPV is probably a reflection of the fact that the viral protein E6 is able to functionally inactivate p53 protein. A variety of molecular markers for cervical cancer are under preliminary investigation, including telomerase (Box: *Telomeres and Telomerase*, p108), which appears to be expressed in most cervical epithelial neoplasias and *KRAS* (mutations having been detected in DNA extracted from cervical aspirates) [10]. Loss of heterozygosity on chromosome 3p has been observed in invasive and pre-invasive lesions [11] suggesting the presence of a tumour suppressor gene; the *FHIT* gene (fragile histidine triad) has been mapped to 3p14.2 (a suspected HPV integration site which is commonly altered in cervical cancer).

Management

Cervical intraepithelial neoplasms may be treated by local excision (wire loop electrode, conisation with laser or scalpel) or destruction (laser vapourisation, radical diathermy or cryocautery). Methods which

do not produce a tissue specimen for histology may ablate an undetected adenocarcinoma *in situ* or microinvasive carcinoma [12]. Recurrences or persistent residual disease may occur.

For early stage invasive carcinoma, where the cancer is confined to the cervix or spread to the upper vagina, surgery and radiotherapy are the primary treatment options. Radiotherapy is usually employed for patients with advanced disease and external beam therapy is used initially for patients with bulky tumours. The use of an intracavity radium source is being replaced with caesium-137, which is considered safer. Radiotherapy may be given postoperatively to patients at a high risk of recurrence (although benefits are not proven) [13].

Unresectable lymph node metastases are a risk factor for persistent disease. Invasive carcinoma of the cervix may follow a more rapidly progressive course in HIV-positive women. Despite initial treatment and even hysterectomy, cervical intraepithelial neoplasia and even invasive cancer may still recur, or residual disease may persist. Common sites of recurrence are the paraortic lymph nodes, liver, lungs, abdomen, bones, the central nervous system and supraclavicular lymph nodes. Recent treatment advances include high dose rate brachytherapy, refinement of treatment dose to minimize failure rate, and addition of chemotherapy concurrently with radiotherapy to minimize local and distant failures. Palliative treatment of those with advanced or metastatic disease may consist of combination platinum-based chemotherapy [14].

Survival from cancer of the cervix depends on stage of disease, with 70-85% of localized cancer cases surviving five years compared to less than 10% of cases with distant spread. Important differences are present in relation to age and ethnic or socioeconomic characteristics, probably as a consequence of differential access to medical care. Survival rates for all stages also vary between regions; even in developing countries, where many cases present at relatively advanced stage, survival rates reach 49% on average (Fig. 5.62). The poorest survival is estimated for Eastern Europe.
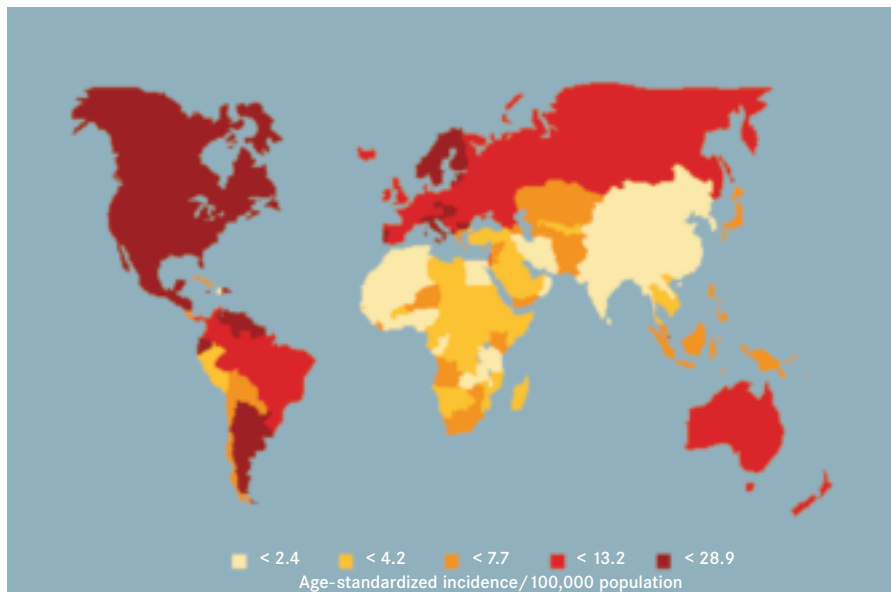
Fig. 5.63 The global incidence of endometrial cancer. Affluent populations are predominantly affected.

< 2.4	< 4.2
< 7.7	< 13.2
< 28.9	

Age-standardized incidence/100,000 population

UTERINE CANCER

Definition
Tumours of the uterine corpus are predominantly adenocarcinomas, arising from the endometrium, or lining, of the uterus.

Epidemiology
Cancer of the uterus is the seventh most common cancer of women with 189,000

	% survival
Netherlands	86
USA (White)	85.8
Khon Kaen, Thailand	78.7
Finland	77
Shanghai, China	76.8
Osaka, Japan	75.9
Italy	75
England	73
Poland	72
Chiang Mai, Thailand	69.5
Cuba	60.9
USA (Black)	58.9

Fig. 5.65 Five-year relative survival rates after diagnosis of cancer of the uterus.

new cases and 45,000 deaths occurring worldwide each year; about 60% of these occur in more developed countries. The highest incidence rates are in the USA and Canada, while other regions with age-standardized rates in excess of 10 per 100,000 include Europe, Australia and New Zealand, the southern part of South America, and the Pacific Island nations. Low rates occur in Africa and Asia (Fig. 5.63).

Some countries, such as the USA and Canada, are experiencing a clear decline in incidence and mortality from cancer of the uterus, particularly among young women. In Europe, rates appear stable in the south and to be decreasing in the north. Uterine cancer occurs primarily in elderly women, the median age of onset being around 60 years old; only 5% of cases develop before age 40.

Etiology
Cancer of the endometrium is linked to reproductive life with increased risk among nulliparous women and women undergoing late menopause (*Reproductive factors and hormones*, p76). The endometrium is normally a hormonally responsive tissue, responding to estrogens with growth and glandular proliferation and to progesterones with maturation. Exogenous estrogens, as in unopposed

estrogen therapy for menopause or prior oophorectomy, increase the risk of cancer whereas oral contraceptives containing an estrogen-progesterone combination decrease it. Syndromes of increased endogenous estrogen exposure, such as granulosa-theca cell tumours of ovary and polycystic ovary, are also associated with an increased risk. Other risk factors include a history of colon or breast carcinoma. Use of tamoxifen as a therapeutic or chemopreventive agent is a risk factor [15]. The disease is clearly associated with obesity, diabetes and hypertension.

Detection
The most common sign is metrorragia (uterine bleeding), especially after menopause. Irregular or postmenopausal bleeding is the presenting symptom in at least 75% of patients. At the time of diagnosis, 75% of patients have disease confined to the uterus although up to 20% of patients have no symptoms [16, 7].

Other signs include those linked to a mass in the lower abdomen, such as dysuria (difficult urination), constipation or bloating. Histological sampling of the endometrium and cervix, either through biopsy or dilation and curettage, should be undertaken in the event of symptoms. Endovaginal echography and hysteroscopy are useful adjuncts in the diagnosis of endometrial pathology.

Pathology and genetics
Endometrioid adenocarcinoma (Fig. 5.64) is the most common histology (60-65%). This tumour type is characterized by the disappearance of stroma between abnor-
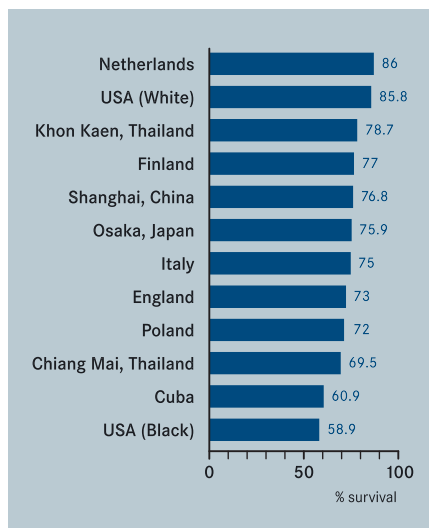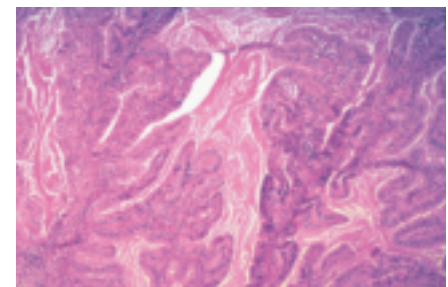

Fig. 5.64 A well-differentiated mucus-secreting endometrial adenocarcinoma with a glandular architecture.
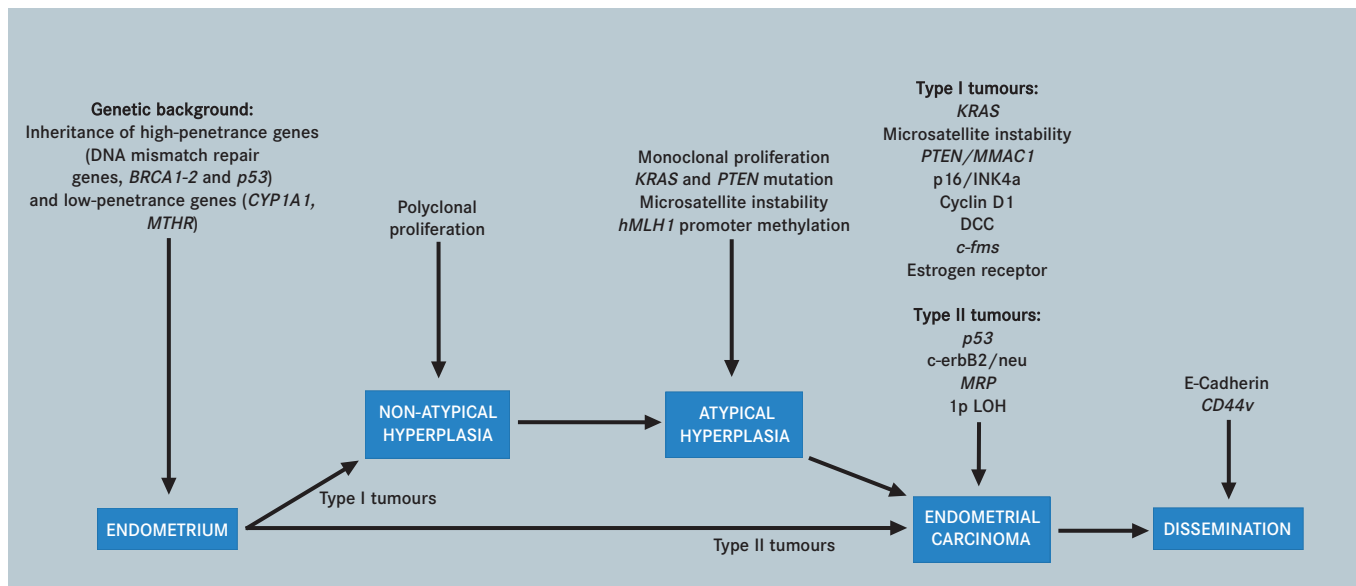
Fig. 5.66 A genetic model for endometrial tumorigenesis.

mal glands that have infoldings of their linings into the lumens, disordered nuclear chromatin distribution, nuclear enlargement, a variable degree of mitosis and is associated with necrosis and haemorrhage [16]. Adenosquamous carcinoma, which comprises 7% or less of cases, has a poor prognosis. 5-10% of endometrial carcinomas are uterine papillary serous carcinomas, a very virulent type. Clear cell carcinoma is more frequent in older women.

Endometrial cancer is a significant risk for women affected by the dominantly inherited hereditary nonpolyposis colorectal carcinoma (HNPCC) syndrome and by Li-Fraumeni syndrome, due to germline mutations in mismatch repair genes and *p53* respectively [17]. An enhanced susceptibility to endometrial cancer has also been linked with an insertional *p53* mutation, a rare mutant in the methylenetetrahydrofolate reductase gene and certain germline variants of the *CYP1A1* gene.

Endometrial tumours which occur in pre- and perimenopausal women and are estrogen-related, with hyperplasia ante- cedent (adenomatous and atypical adenomatous hyperplasias) are of stable behaviour (Type II). Non-endometrioid tumours which appear in postmenopausal women tend to have a virulent behaviour (Type I). A model

for the genetic alterations involved in endometrial tumorigenesis is becoming characterized (Fig. 5.66). Patients with lesions which are positive for cytoplasmic estrogen and progesterone receptors have a better rate of disease-free survival than those with no identifiable receptors [16]. *PTEN* mutations are associated with a more favourable prognosis; tumours with *PTEN* mutations tend to be of endometrioid histology as opposed to clear cell serous cell types and have fewer *p53* mutations. Aneuploidy is associated with poor prognosis, as is the overexpression of c-erbB2/neu and p53 and mutations of codon 12 or 13 of the *KRAS* gene. Decreased expression of CD44 and E-cadherin are associated with metastasis and depth of myometrial invasion.

Management

Pre-cancerous lesions of the endometrium and *in situ* tumours are treated by simple hysterectomy. For frank carcinoma, total abdominal hysterectomy and bilateral salpingo-oophorectomy (removal of the fallopian tubes and ovaries) are the definitive treatment, although tailoring of therapy to meet individual needs is important. More than 50% of recurrences occur in the first two years post-surgery. Thus regular and

frequent follow-up is recommended. Postoperative radiation therapy is currently given to patients at a high risk of relapse following surgery. In inoperable cases, pelvic radiation therapy, usually external beam and intracavity irradiation, may be the sole treatment [16].

High levels of expression of MDR1 protein (multi-drug resistance) or associated proteins in a large number of endometrial tumours and normal endometrial tissues suggest there is a neoplasm which is intrinsically resistant to chemotherapy [18] (Box: *Resistance to cancer chemo- therapy*, p285). In fact, use of chemo- therapy is restricted to those with advanced or recurrent metastatic disease, although cisplatin, doxorubicin and cyclophosphamide or a combination of methotrexate, vinblastine, doxorubicin and cisplatin can produce high response rates and prolonged remissions. Response to high dose progesterone therapy in receptor-positive patients is about 70%. Estrogen-replacement therapy is recommended initially only in patients with *in situ* disease or with low risk stage I tumours.

Survival is usually good, overall around 75-85% and for localized disease up to 90% (Fig. 5.65), although there is some evidence to suggest that black women
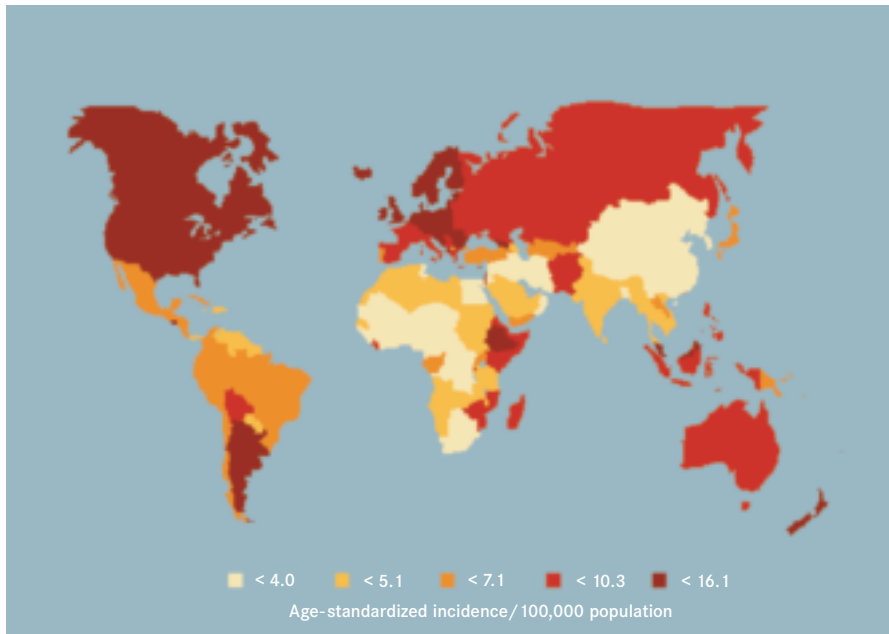
Fig. 5.67 The global incidence of ovarian cancer. This cancer occurs predominantly in developed countries.
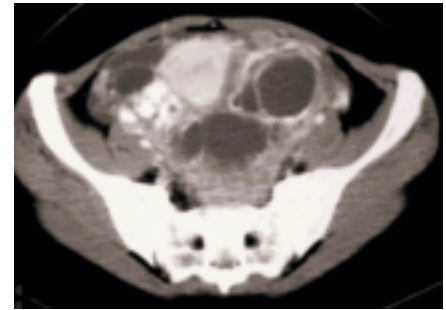

Fig. 5.68 Magnetic resonance image (MRI) of a large, partly cystic ovarian carcinoma.

Fig. 5.69 Surgical specimen of a bilateral ovarian carcinoma (OC). UT = uterus.

have a poorer prognosis for survival from endometrial carcinoma than their white counterparts.

OVARIAN CANCER

Definition
The majority of ovarian cancers are carcinomas, which arise from the surface epithelium of the ovary.

Epidemiology
About 190,000 new cases and 114,000 deaths from ovarian cancer are estimated to occur annually. The highest rates are reported in Scandinavia and Eastern Europe, the USA, and Canada. Low rates are found in Africa and Asia (Fig. 5.67).
The risk of epithelial tumours increases with age, occurring predominantly in peri- and postmenopausal women. Tumours of germinal or embryonic origin are more frequent in young adults.

Etiology
Although most ovarian cancers are sporadic, a family history is the single most important risk factor for ovarian cancer (5-10% of cases), risk being increased four-fold in women with an affected first-degree relative. Cancer of the ovary is influenced by hormones and reproductive factors (*Reproductive factors and hormones*, p76). Risk is slightly increased with nulliparity and a personal history of breast cancer. Decreased risk follows the use of oral contraceptives. In contrast, hormonal treatment for infertility entails an increased risk, whereas treatment at the menopause is only associated with a small risk. Early menarche or late menopause may also entail a slightly increased risk [18]. Diet plays a role, with increased risk linked to obesity and height, as well as some nutritional factors (e.g. lactose). A history of pelvic inflammatory disease, polycystic ovary syndrome and endometriosis have also been associated with increased risk, whilst tubal ligation and hysterectomy may decrease risk.

Detection
The great majority of patients with epithelial ovarian cancer present with disease that has spread outside of the ovary and even the pelvis [19]. Symptoms may include abdominal discomfort, bloating, abnormal vaginal bleeding and gastrointestinal or urinary tract abnormalities. Abdominal and vaginal ultrasonography may suggest the presence of an ovarian tumour, but definitive diagnosis requires laparotomy and biopsy. Pelvic ultrasonography, tumour markers and clinical examination have proved ineffective in mass screening [7] and are employed only for patients having a high familial risk of ovarian cancer. The comparison of molecular profiles generated by laser capture microdissection is hoped to identify patterns of proteins which are uniquely expressed in early disease in order to generate valuable markers for early detection [20].
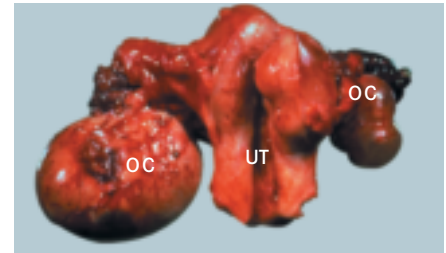
Pathology and genetics
Most ovarian tumours are of epithelial origin and include serous (45% of epithelial tumours), mucinous, endometrioid (Fig. 5.70) and clear cell adenocarcinomas, as well as the rare Brenner tumour. Non-epithelial tumours, including germ cell tumours, gonadal-stromal tumours and tumours which have metastasized to the ovary, are less common. Three categories of lesions are recognized: benign, low malignancy potential or

invasive malignant. Malignant germ cell tumours are uncommon.

A majority of familial ovarian cancer seems to be due to mutations in the *BRCA1* and *BRCA2* genes, which are also associated with a predisposition for breast cancer (*Genetic susceptibility*, p71), (although *BRCA1* is also mutated in a minority of sporadic tumours [18]). Familial syndromes linked to increased risk of ovarian cancer include breast-ovarian cancer syndrome, rare families who present with ovarian cancers only and Lynch type II syndrome, which is characterized by inheri-tance of nonpolyposis colorectal cancer (*Colorectal cancer*, p198), endometrial can-cer and ovarian cancer and is linked to muta-tions in DNA mismatch repair genes *MSH2*, *MLH1*, *PMS1* and *PMS2* (*Carcinogen activa-tion and DNA repair*, p89)[18,19]. Prophylactic oophorectomy is a potential option for geneti-cally high-risk women.

The *ERBB2 (HER-2/neu)* oncogene is overex-pressed in about 30% of ovarian tumours, as is *C-MYC* [21]. *KRAS* mutational activation is also implicated in ovarian cancer. *p53* mutations have been found in 50% of cases.
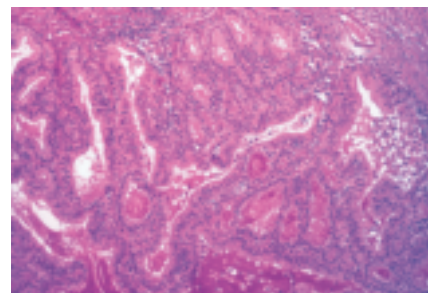

Fig. 5.70 Histopathology of a well-differentiated, mucus-secreting, endometrial-like adenocarcino-ma of the ovary.

MULTICULTURAL ISSUES

Although incidence of cancer is often recorded with reference to national or oth-erwise large populations, the disease bur-den is rarely distributed uniformly across such groupings. This becomes apparent when consideration is given to specific minority groups within a wider communi-ty. A number of variables may contribute to such an outcome. One such variable, genetic make-up, is not amenable to inter-vention but nonetheless may have an impact. For example, there are large racial/ethnic differences in prostate can-cer risk, with high rates of incidence in African-Americans, which may be partly related to genetic differences in hormone metabolism (Farkas A et al., *Ethn Dis,* 10: 69-75, 2000). However, mutations which confer susceptibility to cancer may be car-ried by individuals from any and all ethnic groups (Neuhausen SL, *Cancer,* 86: 2575-82, 1999).

In many instances, there are clear indica-tions that in some ethnic minorities, immi-grant populations and the poor and disad-vantaged, the burden of cancer is greater than that of the general population (e.g. Kogevinas M et al., *Social inequalities and cancer,* Lyon, IARCPress, 1997). In the USA, for example, whilst incidence and mortality rates for some cancers have decreased in the population overall, rates have increased in some ethnic minority groups. The mortality rate for cancer at all sites in white people in 1990-96 was 167.5 per 100,000 whilst in the black population it was 223.4. The reasons for such differences are likely to be complex and multifactorial.

Environmental/behavioural factors may dif-fer between ethnic/cultural groups. For instance, the diet to which some migrant populations are accustomed (e.g. small quantities of red meat, large quantities of fruit and vegetables) may be protective in relation to risk of colorectal cancer, but risk increases with the adoption of a Western diet (e.g. Santani DL, *J Assoc Acad Minor Phys,* 10: 68-76, 1999).

Timely visits to a medical practitioner and participation in screening programmes are critical for early detection and initiation of treatment. Language may be a barrier to understanding health issues. Women from certain ethnic and racial minorities are less likely to take up invitations to participate in breast or cervical screening programmes. This may be partly attributable to the novel-ty of the concept of preventive health, unfa-miliarity with the disease, or with the health system, as well as modesty and religious/cultural barriers. Women of lower socioeconomic status tend to present with a more advanced stage of breast cancer than women of higher socioeconomic sta-tus. African-American, Hispanic, American Indian and Hawaiian women also tend to present with a more advanced stage of breast cancer than white women (e.g. Hunter CP, *Cancer,* 88: 1193-202, 2000). In the USA, women who do not subscribe to private health insurance are less likely to undergo screening for breast, cervical and colorectal cancers (Hsia J et al., *Prev Med,* 31: 261-70, 2000). Such differences involv-ing increased incidence provide an oppor-tunity for strategic action.

Treatment and its outcome may also be affected by ethnic and social differences. For example, the way that pain is per-ceived and dealt with is influenced by the ethnocultural background of the patient (Gordon C, *Nurse Pract Forum,* 8: 5-13, 1997). Ethical dilemmas can develop in multicultural settings due to differing cul-tural beliefs and practices. More research into the relationship between ethnicity and accessibility of medical care, patient support, survival, and quality of life is needed (Meyerowitz BE, *Psychol Bull,* 123: 47-70, 1998).

Recognition of multicultural issues is becoming more widespread. The NCI has launched an initiative to investigate the reasons for disparities in cancer in minor-ity populations (the "Special Populations Networks for Cancer Awareness Research and Training", Mitka M, *JAMA,* 283: 2092-3, 2000). Many areas have units designed to improve equality of access to health care (e.g. NSW Health Multicultural Health Communication Service, http://www.health.nsw.gov.au).
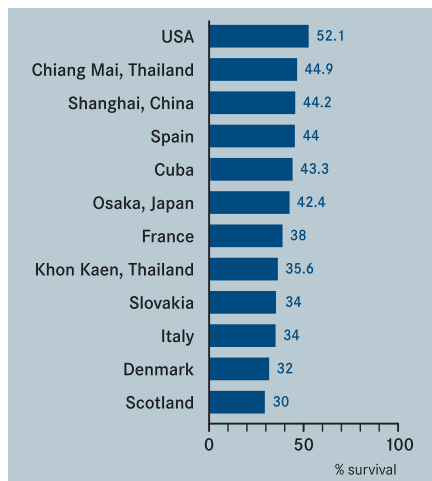
Fig. 5.71 Five-year relative survival rates after diagnosis of ovarian cancer.

Management

Surgery is most often the first recourse in diagnosis and treatment. Treatment of early disease includes bilateral salpingo-oophorectomy and total abdominal hysterectomy, total omentectomy, appendectomy, collecting samples of peritoneal washings for cytological analysis and possibly removal of pelvic retroperitoneal and aortic lymph nodes. Reproductive function and fertility may be conserved in patients with a unilateral, low-grade, unruptured epithelial ovarian tumour. Advanced stage ovarian cancer requires cytoreductive surgery to remove all gross tumour, followed by chemotherapy. External beam radiotherapy may play a limited role in selected patients with minimal residual disease. Intraperitoneal implants may be used as adjuvant treatment for high-risk patients with early disease.

A standard chemotherapy for advanced stage ovarian cancer using cisplatin and paclitaxel achieves response rates of up to 60-80%. Germ cell tumours are very sensitive to chemotherapy and may be treated with vincristine, actinomycin and cyclophosphamide; cisplatin, vinblastine and bleomycin; or cisplatin, etoposide and bleomycin. Recurrent ovarian cancer may be treated with cytoreductive surgery plus chemotherapy and palliative radiotherapy. Hormonal therapy may include progestational agents and anti-estrogens.

Tumour stage (determined surgically) is the most important prognostic factor. Clear cell and small cell carcinomas are associated with a worse prognosis than other histological types. Aneuploidy has been linked to poor survival. In the assessment of response to treatment, decrease in serum CA-125 measurements indicates a more favourable prognosis. Early stage disease has a very good prognosis. Overal five-year survival rates for all stages combined (Fig. 5.71) range from 30-50%. Most women, however, present with late stage disease which is associated with a five-year survival rate of about 20%.

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WEBSITES

NCI Homepages for Cervical Cancer, Endometrial Cancer and Ovarian Cancer:
http://www.cancer.gov/cancer_information/cancer_type/

The Alliance for Cervical Cancer Prevention:
http://www.alliance-cxca.org/

National Ovarian Cancer Coalition (USA):
http://www.ovarian.org/

OESOPHAGEAL CANCER

SUMMARY

> Cancer of the oesophagus is the sixth most common cancer worldwide (more than 400,00 cases per year). Incidence varies markedly, and is highest in Western and South Central Asia.

> Squamous cell carcinoma is most common in developing countries, and is typically associated with tobacco smoking and alcohol abuse. Other risk factors include consumption of very hot beverages and malnutrition.

> Adenocarcinoma occurs predominantly in white men from developed countries, the most important etiological factors being obesity and chronic gastro-oesophageal reflux.

> Most cancers of the oesophagus are detected at an advanced stage; five-year survival rates are less than 15%.

< 1.9   < 3.2   < 5.9   < 10.0   < 38.7

Age-standardized incidence/100,000 population
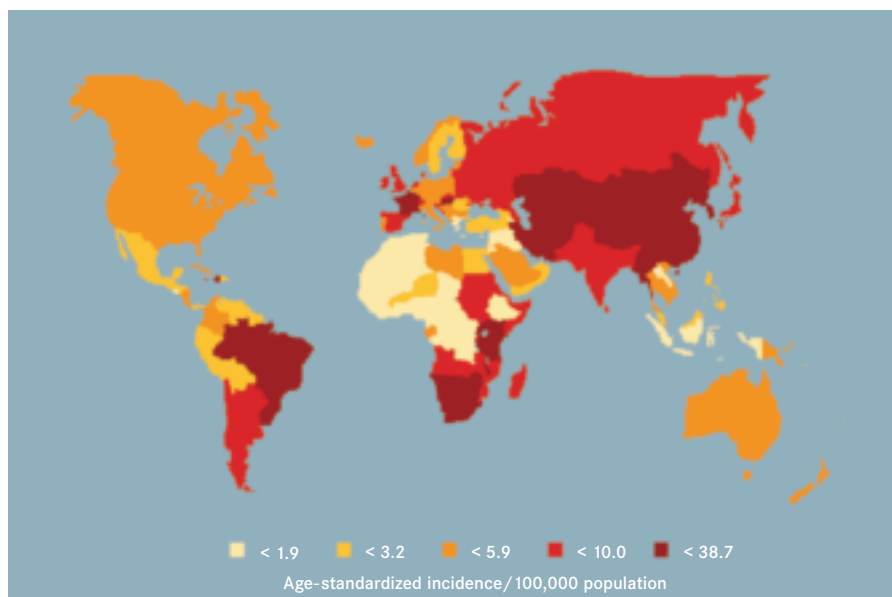
Fig. 5.72 The global burden of oesophageal cancer in men. High incidence rates occur in Northern Iran, the Central Asian republics, North-Central China, parts of South America and in Southern and Eastern Africa.

Definition

The great majority of oesophageal cancers (over 95%) are either squamous cell carcinomas or adenocarcinomas. Tumours of the cardia, which arise within the gastro-oesophageal junction, are sometimes classified in the same group as adenocarcinomas of the oesophagus.

Epidemiology

Cancers of the oesophagus are the sixth most frequent cancers worldwide. In 2000, the number of deaths due to oesophageal cancer amounted to some 337,500 out of a total of 6.2 million cancer deaths worldwide. About 412,000 cases of cancer of the oesophagus occur each year, of which over 80% are in developing countries. While squamous cell carcinoma occurs at high frequency in many developing countries, adenocarci-

noma is essentially a tumour of more developed, industrialized countries.

The differences between incidence of oesophageal cancer in distinct geographical areas are more extreme than observed for any other cancer. Regions of high incidence of squamous cell carcinoma in Asia [1] stretch from the Turkoman plain in northern Iran through the central Asian republics to Henan province in North-Central China, characterized as the "oesophageal cancer belt" (Fig. 5.72). Incidence rates are as high as 200 per 100,000 and in some areas there is a female predominance. Other high-incidence areas are found in parts of South America and in Southern and Eastern Africa. Even within these high-risk areas, there are striking local variations in risk. Studies of migrant populations suggest that when they move to areas of low-risk, they lose their high rates, confirming the importance of local environmental factors in causation.

In Europe and the USA, the age-standardized annual mortality from squa-

mous cell carcinoma is up to five in males and one in females per 100,000 population. However, in particular areas, such as Normandy and Brittany in France and in the north-east of Italy, the incidence rates are much higher in males (up to 30 per 100,000), while remaining relatively low in females. The incidence of adenocarcinoma is steadily increasing in Europe and the USA at a rate of 5-10% per year. This type of cancer now accounts for more than 50% of all oesophageal cancers in the USA and in some European countries [2]. Trends in incidence of all oesophageal cancers vary greatly (Fig. 5.75).

Etiology

Consumption of tobacco and alcohol, associated with low intake of fresh fruit, vegetables and meat, is causally associated with squamous cell carcinoma of the oesophagus worldwide. However, the relative contribution of these risk factors varies from one geographic area to another. In more developed countries, it is esti-

Fig. 5.73 Drinking the scalding beverage *maté* is associated with an increased risk of oesophageal cancer.
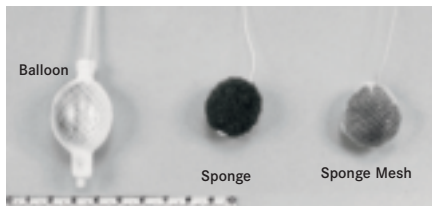

Fig. 5.74 Devices used to collect histological samples from the oesophagus, used for screening in Iran.

mated that 90% of squamous cell carcinomas are attributable to tobacco and alcohol, with a multiplicative increase in risk when individuals are exposed to both factors [3]. The consumption of scalding hot beverages, such as *maté* in South America (Fig. 5.73), is a risk factor [4], malignancy

being the outcome of chronic mucosal injury. Other risk factors include consumption of pickled vegetables, betel chewing in South East Asia, and oral consumption of opium by-products in the Caspian Sea area. Conflicting reports have proposed a role for human papillomaviruses in squamous cell carcinoma [5]. Other environmental risk factors include nitrosamines, food contamination with fungi such as *Geotrichum candidum* and *Fusarium sp.* (*Food contaminants*, p43) and deficiency of vitamins A and C, molybdenum, copper and zinc.

Adenocarcinoma of the oesophagus has been associated with chronic gastro-oesophageal reflux, which most often underlies repetitive mucosal injury and predisposes to metaplasia [6]. This tumour type is directly associated with Barrett oesophagus, a premalignant lesion.

Detection

Although endoscopic or cytologic screening may be useful for early diagnosis in regions of high incidence, there are no widely accepted protocols for such interventions. Cytologic screening of high-risk asymptomatic populations is carried out in China with a swallowed balloon catheter and in Japan with a swallowed encapsulated brush (Fig. 5.74). Endoscopic dye-staining with Lugol's iodine or toluidine blue aids detection of early lesions.

The vast majority of patients initially complain of progressive dysphagia, which may not become apparent until some two-thirds of the lumen has been obstructed, especially in the case of squamous cell carcinoma [7]. Regurgitation and pain on swallowing are frequent, as is weight loss. Laryngeal nerve involvement may be indicated by hoarseness. Patients with adenocarcinomas of the cardia may also suffer from gastrointestinal bleeding [8]. A barium swallow (ingestion of liquid containing barium prior to X-ray) (Fig. 5.76) may indicate narrowing or mucosal irregularity, whereas a chest X-ray may reveal late signs such as the presence of a mass, tracheal compression, aspiration pneumonia or metastases. Endoscopic ultrasonography is currently the most accurate staging method, but is not widely available. CT scanning remains the mainstay of staging prior to resection, supplemented by laparoscopy (for lower one-third cancers) or bronchoscopy (for upper one-third cancers).

Pathology and genetics

Squamous cell carcinoma (Fig. 5.77) develops from squamous epithelium according to a classical dysplasia-carcinoma sequence (*Multistage carcinogenesis*, p84). The most common site of squamous cell carcinoma is the middle third of the oesophagus. Microscopically, most squamous tumours contain islands of
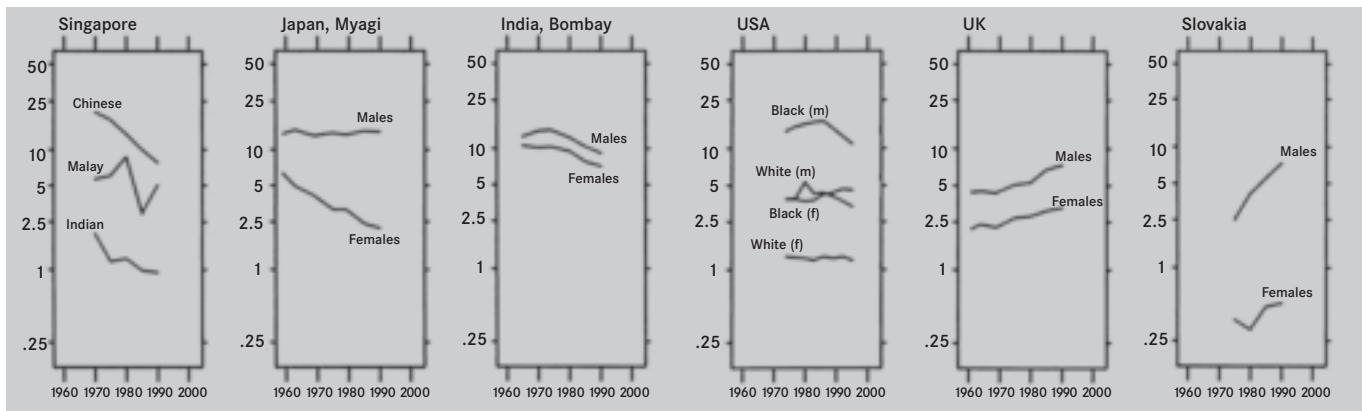

Fig. 5.75 Trends in incidence of oesophageal cancer differ considerably according to geography and reflect differences in prevalence of the two main histological types. D.M. Parkin et al. (2001) *Eur J Cancer*, 37 Suppl. 8: S4-66.
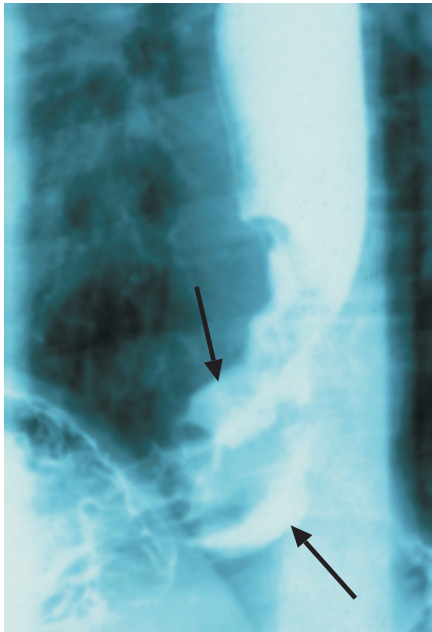
Fig. 5.76 A radiographic view of an oesophageal cancer taken following a barium swallow. Arrows indicate a filling defect caused by obstruction by the tumour.

in 35-70% of tumours, depending on geographic origin. Tumours from high-incidence areas of Western Europe show a high proportion of mutations at A:T base pairs. These mutations may reflect a contribution of metabolites of alcohol. In East Asia, mutations at A:T base pairs are less common, but transversions at G:C base pairs occur at a higher rate than in Western Europe [10]. Mutations in *p53* have been observed in dysplasia, and in normal mucosa adjacent to cancer lesions [11].

In squamous cell carcinoma, other commonly mutated genes are those encoding proteins involved in the control of the G1/S cell-cycle checkpoint, such as cyclin D1 and p16^{INK4A} (*Cell cycle*, p104). Amplification of the cyclin D1 gene *CCDN1* (11q13) occurs in 20-40% of tumours. The gene encoding p16^{INK4A} is often subject to hypermethylation of the promoter region, resulting in down-regulation of expression. Amplification of a number of proto-oncogenes (*HST-1, HST-2, EGFR, MYC*) has also been reported [12]. In the Japanese population, a polymorphism in the gene encoding aldehyde dehydrogenase 2 (*ALDH2*), which plays a role in ethanol metabolism, is significantly associated with squamous cell carcinoma [13].

Adenocarcinoma of the oesophagus mostly occurs within the distal third of the oesophagus and is preceded by a
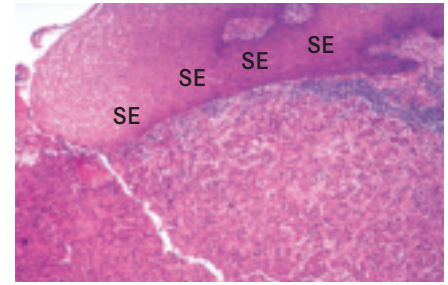

Fig. 5.77 Moderately differentiated squamous cell carcinoma of the oesophagus, ulcerated, deeply invasive and extending below the normal squamous epithelium (SE).

well-defined preneoplastic lesion called Barrett mucosa (or Barrett oesophagus) (Fig. 5.79). Barrett mucosa is a glandular, metaplastic mucosa of the normal squamous epithelium. It is often associated with chronic gastro-oesophageal acid reflux. However, it also occurs in the context of chronic biliary alkaline reflux, as well as, in some cases, the absence of a detectable reflux. Men are seven times more commonly affected than women [14].

The estimated risk of developing an adenocarcinoma for patients with Barrett mucosa is 30-125 times greater than in the general population. There are three subtypes: fundic (base of oesophagus), cardiac (the region between the oesophagus and the stomach), and intestinal.
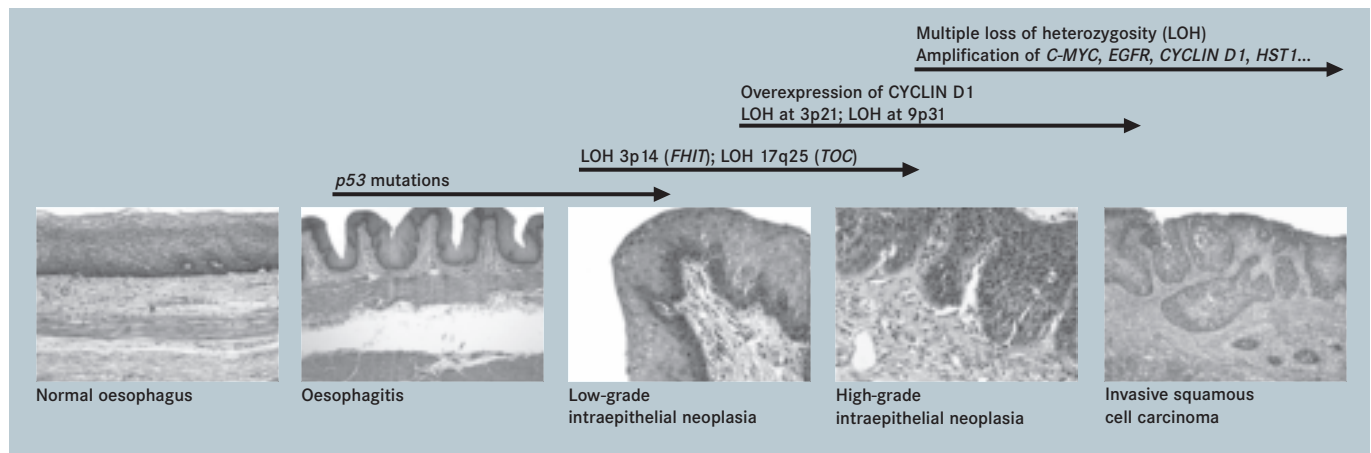
atypical squamous cells which infiltrate the underlying normal tissue and contain keratin pearl formation and intercellular bridges [9].

The sequence of genetic events leading to squamous cell carcinoma is only partially understood (Fig. 5.78). Mutation of the *p53* gene is an early event, detected

Fig. 5.78 Sequence of genetic alterations in the development of squamous cell carcinoma of the oesophagus.

Factor	Alteration
Tumour suppressor genes *p53*	60% mutation – high-grade intraepithelial neoplasia and carcinoma
APC	Late in intraepithelial neoplasia-carcinoma sequence
FHIT	Common, early abnormalities
CDKN2A (p16^{INK4A})	Hypermethylation common in intraepithelial neoplasia
Growth factor receptors CD95/APO/Fas	Shift to cytoplasm in carcinoma
EGFR	Expressed in 60% of carcinomas, gene amplification
c-erbB2	Late in dysplasia-carcinoma sequence, gene amplification
Cell adhesion E-cadherin	Loss of expression in intraepithelial and invasive carcinoma
Catenins	Similar loss of expression to E-cadherin
Proteases UPA	Prognostic factor in carcinoma
Proliferation Ki-67	Abnormal distribution in high-grade intraepithelial neoplasia
Membrane trafficking rab 11	High expression in low-grade intraepithelial neoplasia

Table 5.9 Genes and proteins involved in the development of adenocarcinoma from Barrett oesophagus.
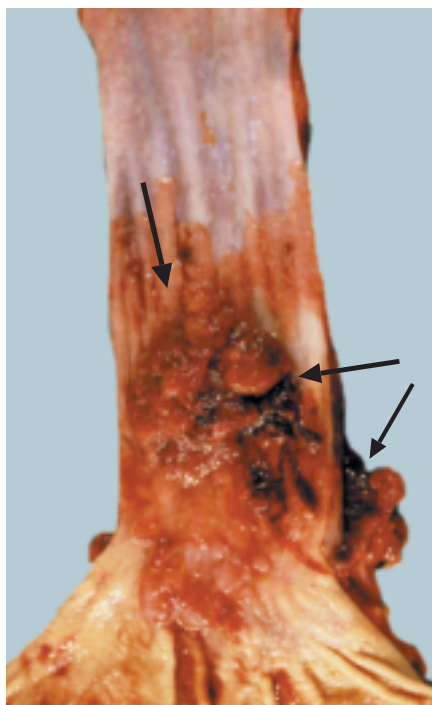

Fig. 5.79 A highly infiltrative adenocarcinoma in a Barrett oesophagus.

Mutation of the *p53* gene is common in the early stages of adenocarcinoma of the oesophagus (Table 5.9). The presence of a *p53* mutation in Barrett mucosa and in dysplasia may precede the development of adenocarcinoma. In high-grade dysplasia, a prevalence of *p53* mutations of approximately 60% is found, similar to that found in adenocarcinoma. Almost half of these are C to T transitions at dipyrimidine sites (CpG islands).

Alteration in transcription of *FHIT* and of p16^{INK4A} may be early events in adenocarcinoma. In contrast, a number of other loci are altered at a relatively late stage with no obligate sequence of events. Prevalent changes (>50%) include loss of heterozygosity on chromosomes 4q, 5q (several loci including *APC*), 17p and amplification of the gene encoding c-erbB2. Molecules involved in membrane traffic, such as rab 11, have been reported to be specific for the loss of polarity (rounding-up of cell nuclei) seen in low-grade dysplasia. In invasive oesophageal adenocarcinoma, reduced expression of the cadherin/catenin complex and increased expression of various proteases is detectable [15].

Management

Endoscopic ultrasonography is used to evaluate both depth of tumour infiltration and para-oesophageal lymph node involvement. In advanced carcinomas, CT and MRI give information about local and systemic spread. Tumour growth is characterized as swelling of the oesophageal wall, with or without direct invasion to surrounding organs. The primary treatment for local disease is oesophagectomy. This surgical approach is rarely curative (eventually 85 to 90% of the patients die of recurrent disease) but palliation of dysphagia is an important secondary objective. Placement of a prosthetic tube or stent across the tumour stenosis (narrowing) may be indicated to restore swallowing in patients not suitable for surgery. Radiotherapy (external beam or brachytherapy) as well as multiple chemotherapeutic protocols have also been proposed (alone or combined with surgery), but these approaches are rarely curative. Palliation with radiation alone is an alternative to surgery, particularly if combined

Fig. 5.80 Five-year relative survival after diagnosis of oesophageal cancer.

with a stent; laser recannulation, alcohol injection and dilation may be used to maintain the oesophageal lumen [8]. Prognostic factors include stage at diagnosis, patient's general health, morphological and molecular features of the tumour, for squamous cell carcinoma the depth of invasion and for adenocarcinoma presence of lymphatic metastases. Overall five-year relative survival rates are poor (Fig. 5.80), survival ranging from about 10% in patients with squamous cell carcinoma to 20% in patients with adenocarcinoma.

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WEBSITE

NCI Esophageal Cancer Homepage:
http://www.cancer.gov/cancer_information/cancer_type/esophageal/

BLADDER CANCER

SUMMARY

> Bladder cancer is the ninth most common cancer worldwide, with 330,000 new cases and more than 130,000 deaths per year.

> Bladder cancer is primarily attributable to smoking, which accounts for 65% of male and 30% of female cases in some developed countries. Other less important causes include analgesic abuse (phenacetin), some types of cancer chemotherapy and, historically, occupational exposure to chemicals such as 2-naphthylamine. In Egypt and some Asian regions, chronic cystitis caused by *Schistosoma haematodium* infection is a major risk factor.

> Treatment based on endoscopy, surgery, radiotherapy and cytotoxic drugs often permits long-term survival in developed countries, where 65% of patients live for at least five years after diagnosis.

Fig. 5.81 The global incidence of bladder cancer in men. Although the majority of cases occur in developed countries, bladder cancer also occurs at high rates in some developing countries, including parts of Northern Africa and South America.

Definition

More than 90% of bladder cancers are transitional cell carcinomas. Much less common are adenocarcinoma (6%), squamous cell carcinoma (2%) and small cell carcinoma (less than 1%).

Epidemiology

Bladder cancer accounts for approximately two-thirds of all urinary tract cancers. By incidence, bladder cancer is the ninth most common cancer worldwide, although in the USA, for example, bladder cancer is the fourth most frequent tumour among men. Approximately 336,000 new cases occurred in 2000, two-thirds of which were in developed countries [1]. Incidence and mortality rise sharply with age and about two-thirds of cases occur in people over the age of 65. The male:female ratio is approximately 3:1. High incidence rates (>12 pe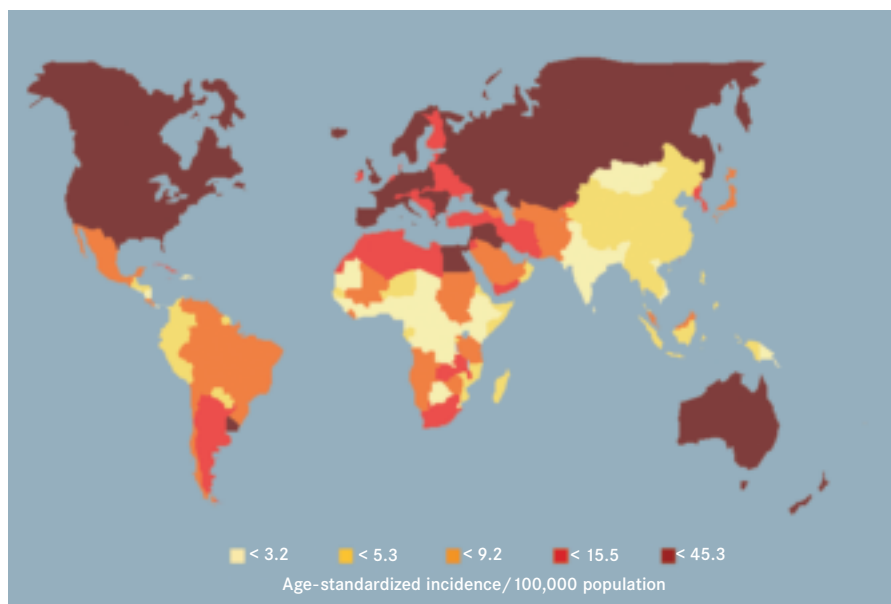r 100,000 men and >3 per 100,000 women) are observed throughout Southern, Western and Northern Europe, North America, Australia, Western Asia, Northern Africa and Uruguay (Fig. 5.81) Bladder cancer incidence is either rising moderately or is steady in most developed countries. About 132,000 people each year die from bladder cancer, men throughout the world having a mortality rate of 10 per 100,000 population, and women 2.4, although these values nearly double for developed countries.

Etiology

The most important risk factor for bladder cancer is cigarette smoking, which accounts for approximately 65% of male cases and 30% of female cases in populations of developed countries [2]. It is likely that smokers of black (air-cured) tobacco are at a greater risk than smokers of blond (flue-cured) tobacco and this may explain some of the disparity observed in European incidence rates and also the high incidence observed in Uruguay. The risk associated with tobacco smoking, and in particular with black tobacco smoking, is likely to be due to the presence in the smoke of aromatic amines including benzidine, 4-aminobiphenyl, 2-naphthylamine and 4-chloro-*ortho*-toluidine. Bladder cancer risk increases approximately linearly with duration of smoking, reaching a five-fold risk after 40 years (Fig. 5.82). The risk also increases with the number of cigarettes smoked, up to approximately 20 cigarettes per day; above that level, no further increase in risk is observed. Upon smoking cessation, a substantial decrease in risk of bladder cancer is observed within several years, implying an effect in late stages of the carcinogenic process.

Work in the rubber and dyestuff industries and specifically occupational exposure to aromatic amines, particularly including 2-naphthylamine and benzidine, are correlated with a high risk of bladder cancer [3]. Exposure to polycyclic aromatic hydrocarbons, polychlorinated biphenyls, formaldehyde, asbestos and solvents, and work in
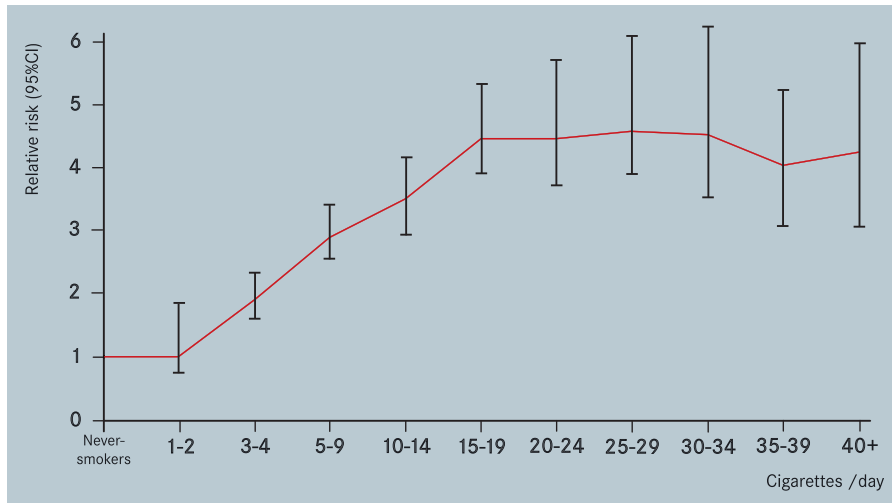
Fig. 5.82 Risk of bladder cancer among men who smoke relative to never-smokers, according to daily cigarette consumption.

Fig. 5.83 A canal in a poor housing district in Egypt. Such canals may provide a habitat for the snails which are host to *Schistosoma* parasites. Chronic infection with *Schistosoma haematobium* causes cystitis and often bladder cancer.
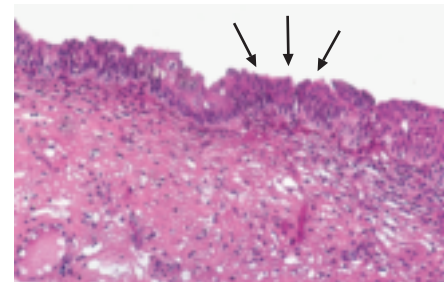

Fig. 5.84 Carcinoma *in situ* of the bladder; the normal transitional epithelium has been replaced by a disorganized, poorly-differentiated cell layer (arrows).
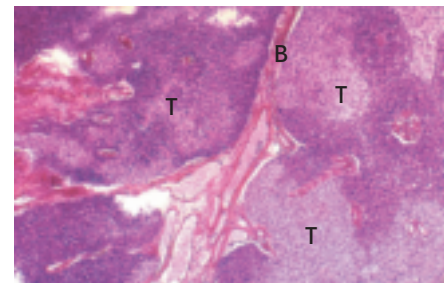

Fig. 5.85 Transitional cell carcinoma of the bladder, moderately differentiated, with a papillary architecture. B = blood vessel, T = tumour.

leather manufacturing, as a painter and as a barber or hairdresser have been variously associated with increased risk. The uncertainty surrounding these associations is partly due to difficulty in measuring past exposure to specific chemical agents.

In common with cancer of the renal pelvis, a consistent relationship has been observed between use of phenacetin-containing analgesics and bladder cancer, with relative risks varying from 2.4 to over 6-fold. Use of the anticancer drug cyclophosphamide, an alkylating agent, has been strongly and consistently linked to bladder cancer. Non-Hodgkin lymphoma patients treated with cyclophosphamide therapy have a dose-dependent increased risk of bladder cancer.

Infection by the trematode worm, *Schistosoma haematobium,* is associated with an up to five-fold increased risk. In endemic areas, which include most of Africa and in several West Asian countries, infection as a result of ingestion of contaminated water occurs from childhood (Fig. 5.83), and risk of bladder cancer, especially of the squamous cell type, increases as from the third decade of life. The infection is responsible for about 10% of bladder cancer cases in the developing world and about 3% of cases overall [4].

Decreased risk of bladder cancer is associated with consumption of foods rich in vitamin A and carotenoids; evidence concerning a risk associated with coffee consumption is inconsistent.

Detection

Detection of neoplastic alterations in exfoliated bladder cells collected in the urine has been proposed as a screening approach for bladder cancer, in particular among industrial workers potentially exposed to aromatic amines, but there is no evidence in favour of its effectiveness. Other methods are also under investigation [5].

Haematuria, usually painless, is the presenting symptom for the majority of patients with bladder cancer. Patients may also present with bladder irritability, including urinary frequency, urgency and dysuria. Diagnosis is made by urine analysis and after visualization of the bladder by ultrasound and cystoscopy. Tissue for histopathological analysis may be obtained through transurethral resection.

Pathology and genetics

Approximately 90% of bladder cancers are classified as transitional cell carcinoma and are believed to originate in intra-epithelial neoplastic transformation of the bladder transitional epithelium. The localized proliferation of transformed cells can give rise to a carcinoma *in situ*, which may take several clinical forms, not necessarily associated with high grade or high risk of progression (Fig. 5.84) [6]. Spread can occur by growth into the submucosa and muscularis of the bladder wall (25% of cases). About 70% of transitional cell carcinomas are of the papillary type (Fig. 5.85) and do not invade the muscularis propria of the bladder wall, 10% are described as nodular and 20% as mixed.

Infection with *S. haematobium* is associated with the development of squamous cell carcinoma and in endemic areas, such as Egypt, this type constitutes 90% of bladder tumours [7].

A number of genes which regulate enzymes involved in the metabolism of bladder carcinogens have been identified and it has been hypothesized that subjects carrying specific genotypes could be at an increased risk of bladder cancer [8]. For example, a dominant mutation in the *NAT2* gene causes slow metabolism of aromatic amines, favouring their transformation into active carcinogens; slow metabolizers may be at a 40% increased risk of bladder cancer. Similarly, individuals who are null for the *GSTM1* gene, which encodes an enzyme involved in the detoxification of polycyclic aromatic hydrocarbons, have been reported to be at increased risk of bladder cancer. There is no evidence for high-penetrance gene mutations that carry an elevated risk of bladder cancer. The oncogene *HRAS* is mutated at codon 12 in about 40% of bladder tumours. Overexpression of the epidermal growth factor receptor is associated with invasive disease. The gene encoding c-erbB2 (*ERBB2*) is amplified in a small proportion of bladder tumours. Cytogenetic and molecular techniques have implicated aberration/partial loss of chromosome 9 as a common feature in bladder cancer, and the cyclin-dependent kinase inhibitors p16^{INK4A} and p15 are also implicated in this context. Altered expression of the phosphorylated form of the retinoblastoma protein is common, and most often encountered in invasive tumours. Nuclear overexpression of p53 protein, essentially attributable to mutation of the gene, is common and is associated with disease progression (Fig. 5.86) [9].

Management

Most patients with carcinoma *in situ* progress to muscle invasion within 10 years, but can achieve good responses to intravesical therapy - the administration of a therapeutic agent directly into the bladder, thereby exposing the mucosa to high drug concentrations [10]. The most commonly used agent in intravesical therapy for superficial transitional cell carcinomas, to prevent recurrence, and possibly decrease progression and improve survival, is bacille Calmette-Guérin (BCG), an attenuated strain of the *Mycobacterium bovis* bacterium which causes tuberculosis. Cytotoxic drugs such as thiotepa, doxorubicin, mitomycin C and/or ethoglucid may be used for superficial tumours to prevent recurrence.

The currently preferred treatment for patients with invasive bladder cancer is radical cystectomy. This involves excision
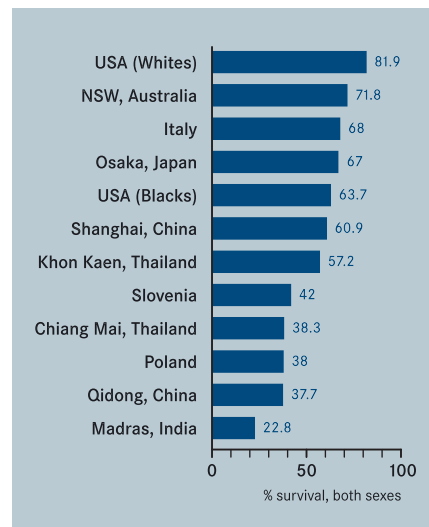
Fig. 5.87 Five-year relative survival rates after diagnosis of bladder cancer.

of the bladder, prostate and seminal vesicles in males or the bladder, ovaries, uterus, urethra and part of the vagina in females. Urinary diversion, and some restoration of bladder function, may be achieved through a range of reconstruction options that continue to be refined and improved. Adjuvant chemotherapy (e.g with cisplatin, methotrexate and vinblastine, or the latter combination plus doxorubicin) may be employed. Several new agents have been identified [11].
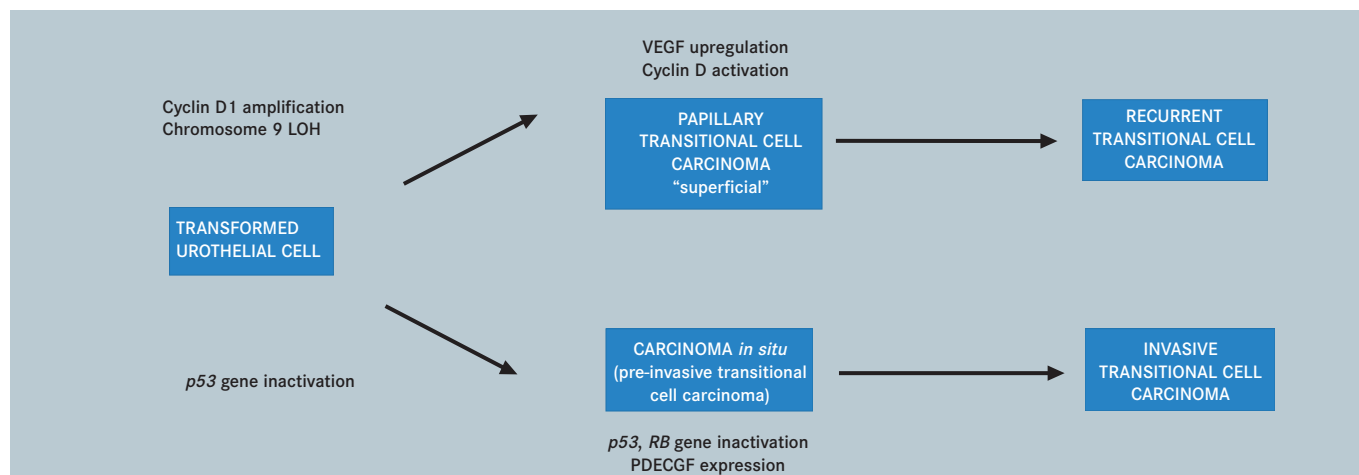
Fig. 5.86 Genetic alterations associated with the development of bladder cancer. LOH = loss of heterozygosity, VEGF = vascular endothelial growth factor, PDECGF = platelet derived endothelial cell growth factor.

Partial cystectomy is appropriate for only a minor proportion of patients with invasive bladder cancer. Radical radiation therapy as sole treatment has been evaluated, and criteria contributing to a favourable outcome (tumour size, stage, morphology, etc.) have been determined. Tumour staging is based on the degree to which the tumour has invaded the bladder wall.

In more developed countries, five-year relative survival is in the order of 65% (Fig. 5.87), and there has been a steady improvement during the last decades. Survival is poorer in developing countries, with five-year relative survival rates of 30-50%.

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NCI Bladder Cancer Homepage.
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HEAD AND NECK CANCER

SUMMARY

> The most common cancer of the head and neck, namely oral cancer, ranks eleventh worldwide (390,000 new cases per year), while cancers of the pharynx (65,000 cases) and larynx (160,000 cases) are less common.

> Head and neck cancers mainly afflict men, with sex ratios exceeding 10:1, and are typically caused by smoking, together with alcohol abuse. In some regions (e.g. India) oral cancer is mainly due to tobacco chewing. Multiple primary carcinomas are not uncommon.

> Early-stage tumours can be surgically resected, but many patients are diagnosed with advanced disease and prognosis is poor. Oral cancer patients have a five-year survival rate of less than 50%.

> Nasopharyngeal cancer is largely restricted to Southern Chinese populations and strongly associated with Epstein-Barr virus infection.

Fig. 5.88 The global incidence of oral cancer in men. Oral cancer is common in India, Australia, Hungary, France, Brazil and Southern Africa.

Definition

Head and neck cancers as described here will be restricted to squamous cell carcinomas of the upper aerodigestive tract (which extends from the surface of the lips to the neck region of the oesophagus) and include the oral cavity, larynx and pharynx (comprising the oropharynx, hypopharynx and nasopharynx). Other tumours which occur in this area, such as those of the brain and thyroid and melanoma, are conventionally dealt with separately (*Tumours of the nervous system*, p265; *Thyroid cancer*, p257; *Melanoma*, p253).

Epidemiology

Cancers of the oral mucosa and oro- and hypopharynx can be considered together, as there are similarities in their epidem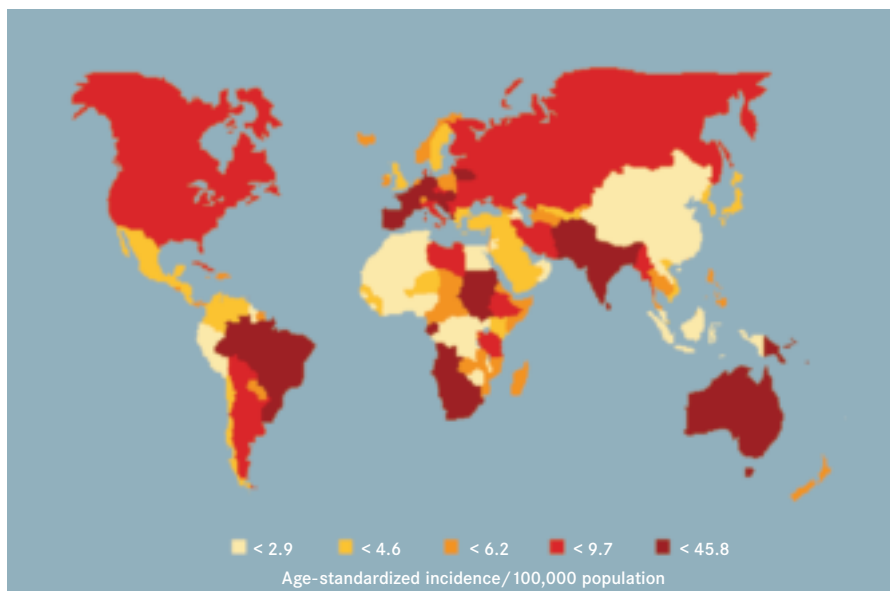iology, treatment and prognosis. The geographic patterns and trends in incidence for these cancers vary depending upon the anatomical sub-sites concerned, a phenomenon that is often explicable by the influence of risk factors, such as tobacco use and alcohol consumption. A high incidence of these cancers is observed in the Indian subcontinent, Australia, France, South America (Brazil) and Southern Africa (Fig. 5.88). Oral cancer is the 11th most common cancer in the world in terms of number of cases, while cancer of the pharynx (apart from nasopharynx) ranks as 20th. Worldwide, about 389,000 new cases occurred in 2000, two-thirds of which were in developing countries, and these cancers are responsible for some 200,000 deaths each year.

The male:female ratio of occurrence varies from 2-15:1 depending on the anatomical sub-site, with extreme ratios characteristic of tongue, floor of mouth and pharyngeal cancers. The highest incidence among males is reported in Bas-Rhin and Calvados in France, whereas among females the highest occurrence is observed in India. Cancers of the mouth and anterior two-thirds of the tongue generally predominate in developing countries, whereas pharyngeal cancers are common in developed countries and in Central and Eastern Europe. In most countries, oral/pharyngeal cancer incidence and mortality rates have either been stable or increasing in the last four decades. Sharp increases in incidence have been reported in Germany, Denmark, Scotland, Central and Eastern Europe, and there are increases in Japan, Australia and New Zealand, and in the USA among non-whites.

New cases of cancer of the larynx occurring worldwide number about 160,000, i.e. about 2% of the total world cancer cases, making laryngeal cancer the 18th most common cancer. The disease is markedly more frequent in males than in females (male:female ratio of 12:1 and 6:1 in developing and developed countries respectively). There is a large geographic variability in disease frequency, high-risk countries being in Southern Europe (France, Italy, Spain), Eastern Europe (Russia, Ukraine), South America (Uruguay, Argentina), and Western Asia (Turkey, Iraq) (Fig. 5.89). Mortality from laryngeal cancer is

poorly known since hypopharyngeal cancer deaths are often mis-certified as deaths from cancer of the larynx.

Carcinomas of the salivary glands and nasopharynx are distinguished from head and neck cancers at other sites both by epidemiology and by etiology. Nasopharyngeal cancer is relatively rare on a world scale (65,000 new cases per year, or 0.6% of all cancers), but it has a very distinctive geographic distribution. Age-standardized incidence rates are high for populations living in or originating from Southern China, whilst populations elsewhere in China, South East Asia, North Africa, and the Inuits (Eskimos) of Canada and Alaska, all have moderately elevated rates (Fig. 5.90). Males are more often affected than females (sex ratio 2−3:1), and in most populations, there is a progressive increase in risk with age. In moderate-risk populations, however, most notably in North Africa, there is a peak in incidence in adolescence. There appears to have been a decrease in incidence over time in some high-risk populations (e.g. Hong Kong).

Etiology

Smoking and drinking are the major risk factors for head and neck cancer in developed countries, in the Caribbean and in South American countries [1-3]. Smoking is estimated to be responsible for about 41% of laryngeal and oral/pharyngeal cancers in men, and 15% in women worldwide and these proportions vary amongst different populations. Tobacco smoking has also been found to be an important risk factor for nasopharyngeal cancer in otherwise low-risk populations. These risk factors have been shown, for laryngeal and oropharyngeal cancers, to have a joint "multiplicative" or synergistic effect.

In the Indian subcontinent, chewing tobacco in the form of betel quid (a combination of betel leaf, slaked lime, areca-nut and tobacco with or without other condiments), bidi (a locally hand-rolled cigarette of dried temburni leaf containing coarse tobacco) smoking and drinking locally brewed crude alcoholic drinks are the major causative factors. The role of betel quids without tobacco is not clear, though a recent case-control study from Pakistan reported a high risk of oral cancer [4]. Reverse smoking (in which the lit
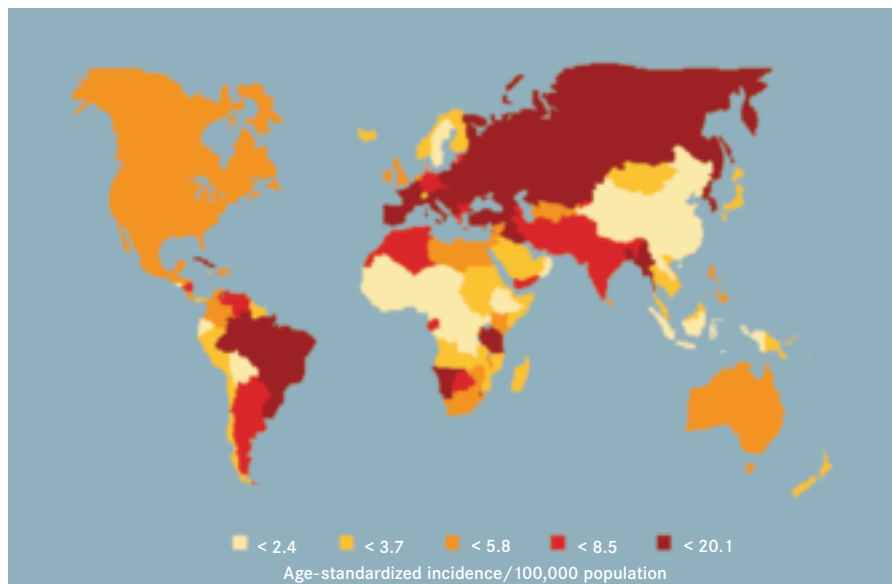

Fig. 5.89 The global incidence of cancer of the larynx in men. High-risk countries are found in Southern and Eastern Europe, Latin America and Western Asia.

end of the cigarette is placed in the mouth so that an intense heat is experienced) is a risk factor for cancer of the hard palate. Oral snuff use is an emerging risk factor for oral cancer, particularly among young males in the USA.

A generally impoverished diet, particularly lacking in vegetables and fruits, is another risk factor for oral cancer [5]. Consistently, studies also indicate a protective effect of a diet rich in vegetables and fruits (20-60% reduction in risk). A high intake of salted fish and meat and the release of nitrosamines on cooking such foods have been linked to nasopharyngeal cancer in endemic regions.

Oral human papillomavirus (HPV) infection (transmitted sexually or perinatally) is associated with an increased risk of head and neck squamous cell carcinoma development [6]. Overall estimates for HPV prevalence in head and neck squamous cell carcinoma are very variable, ranging from 8-100%, but an unusual laryngeal pathologic subtype, verrucous laryngeal carcinoma, has a 100% prevalence of HPV. Tumours of the oropharynx (and in particular, tonsillar tissue) have been found to be three times more likely to be HPV-positive than tumours at other head and neck sites. Women with a history of *in situ* or inva-

sive cervical carcinoma have a two to four-fold increased risk of oral or laryngeal cancer, in addition to increased risks of other cancers associated with HPV. Additional risk factors implicated in cancer of the larynx include chronic laryngitis, chronic gastric reflux and exposure to wood dust, asbestos or ionizing radiation.

Infection with Epstein-Barr virus is important in the etiology of nasopharyngeal cancer. This virus is not found in normal epithelial cells of the nasopharynx, but is present in all nasopharyngeal tumour cells, and even in dysplastic precursor lesions [7] (*Chronic infections*, p56).

Detection

Although many head and neck cancers arise in anatomically accessible areas, delayed diagnosis is common. Symptoms of oral cancer include pain, bleeding, difficulty in opening the mouth, chewing, swallowing and speech, and a swelling in the neck. Early lesions are often painless and present as slightly elevated, velvety red mucosal patches, as punctate lesions, or as indurated small ulcers or growths. In more advanced stages, a large ulceroproliferative mass, with areas of necrosis, and extension to neighbouring

structures such as bone, muscles and skin may be evident. Cancers of the oral cavity may be preceded by, and present with, leukoplakias (Fig. 5.92) or with mucosal rigidity and fibrosis, restricted mouth opening and tongue mobility (oral submucus fibrosis). Some 5-15% of patients with cancer of the lip mucosa present with lymph node metastases, compared with more than 50-70% of those with tongue and floor of the mouth cancers. Distant metastases from oral cancer are uncommon. A careful oral examination and palpation of the neck leads to diagnosis, which is confirmed by biopsy.

Oral visual inspection in high-risk individuals leads to early diagnosis of oral precancer [8,9]. However, the effectiveness of organized screening in reducing incidence of and mortality from oral cancer remains to be established.

An asymptomatic high neck mass in an adult is frequently associated with a primary oropharyngeal (tongue base and tonsil) or hypopharyngeal primary tumour. Fine needle aspiration biopsy and careful direct laryn-

Fig. 5.90 The global incidence of nasopharyngeal cancer in men. This cancer is very common in Southern China.

Fig. 5.91 A paan-tobacco chewer in Kerala, South India, with ingredients for betel quid (betel leaf, areca-nut, lime and tobacco). This habit is associated with a high risk of oral cancer.
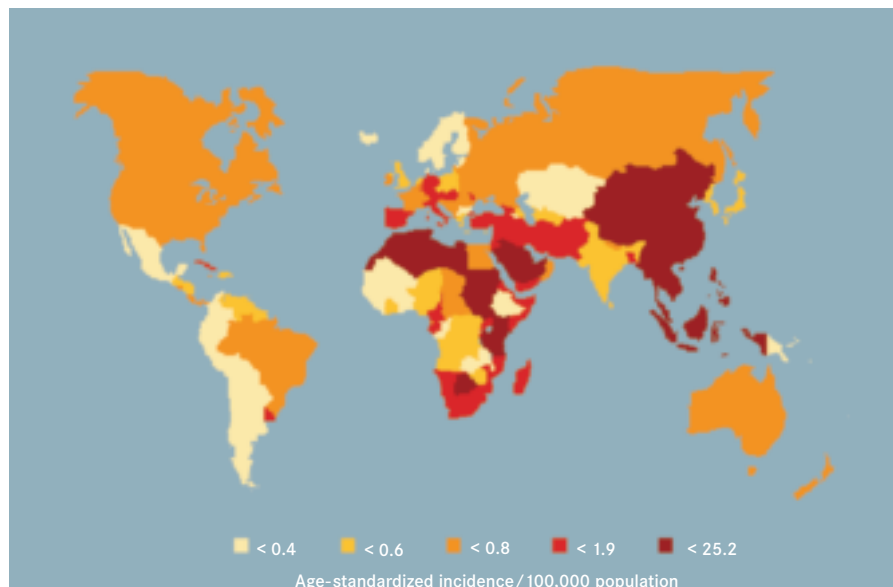
goscopy in order to identify the primary tumour are mandatory. Frequently, a surgical panendoscopy with tonsillectomy is indicated. Patients with pharyngeal cancers may complain of difficulty in swallowing and hoarseness of voice, particularly in advanced stages. The early symptoms of laryngeal cancer are hoarseness with dysphagia, pain and a neck mass. In most cases, the first sign of nasopharyngeal cancer is a mass in the neck (due to lymph node metastasis). Because the tumour is close to the foramina through which several cranial nerves pass, there may be signs due to their compression, as well as pain, blocked Eustachian tubes and nasal stuffiness. Early detection of nasopharyngeal cancer by screening for elevated antibody titres to Epstein-Barr virus has been widely performed in populations of Southern China, although so far, it is not known whether this procedure can prevent deaths.

Pathology and genetics

Most cancers of the head and neck are squamous cell carcinoma, which may be poorly, moderately or well-differentiated, according to the degree of keratinization (Fig. 5.94). Other variants of squamous cell carcinoma include verrucous carcinoma, sarcamoid squamous cell carcinoma and lymphoepithe-

lioma [10]. The vast majority of nasopharyngeal cancers in endemic regions is comprised of non-keratinizing and undifferentiated histological types, whereas in non-endemic countries, some 30-50% are keratinizing squamous cell carcinomas [11].

Conditions carrying increased risk of head and neck cancer include epithelial differentiation disorders, such as dyskeratosis congenita, and DNA repair deficiency syndromes such as Blooms' syndrome, Fanconi anaemia, ataxia telangiectasia and xeroderma pigmentosum (*Carcinogen activation and DNA repair*, p89).

A strong genetic component to the risk of developing nasopharyngeal cancer is evident. Migrant populations of Chinese or North African origin appear to retain their elevated risk, as do their children, born in a new host country. An association between human leucocyte antigen (HLA) profile and risk of nasopharyngeal cancer has been reported, and a study of affected siblings in Singapore identified a gene locus close to HLA with a 20-fold increased risk for nasopharyngeal cancer.

Cytogenetic abnormalities have been reported in head and neck squamous cell carcinoma, including gain or loss of the Y chromosome and abnormalities at other loci; very
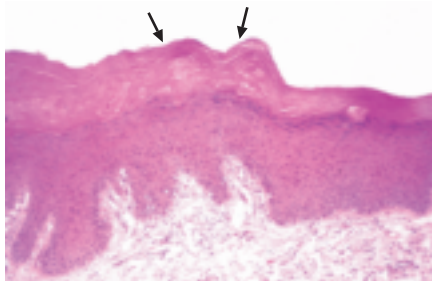
Fig. 5.92 Oral leukoplakia with mild dysplasia; leukoplakia is a precursor to oral cancer.

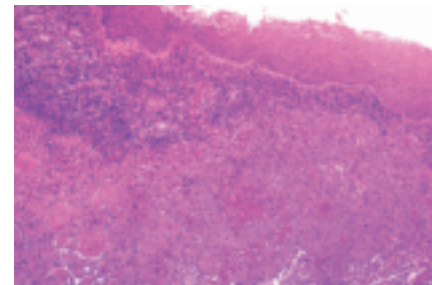Fig. 5.93 A moderately advanced invasive cancer in the buccal mucosa.

Fig. 5.94 A well-differentiated, invasive squamous cell carcinoma of the larynx.

complex karyotypes are frequent [12] (Fig. 5.96). The genetic alterations observed in oral cancer include activation of proto-oncogenes such as cyclin D1, *MYC*, *RAS*, *EGFR* and inactivation of tumour suppressor genes such as those encoding p16^{INK4A} and p53 and other putative suppressor loci [13]. Early changes include loss of tumour suppressor genes on chromosomes 13p and 9p, followed by 17p. *p53* mutations and overexpression are seen in the progression of preinvasive lesions to invasive lesions. *p53* mutations are more frequently reported in developed (40-50%) than in developing countries (5-25%). Tumours from India and South East Asia are characterized by the involvement of *RAS* oncogenes, including mutation, loss of heterozygosity (*HRAS*) and amplification (*KRAS* and *NRAS*). Various genetic polymorphisms in genes such as *GSTM1* or *CYP450A1* are associated with oral carcinogenesis.

Management

Surgery and radiotherapy have been the mainstay of treatment for oral cancer. Those with early or intermediate tumour stages are treated with curative intent with moderate morbidity while those with more advanced disease are treated with definitive radiation therapy and chemotherapy. Radical surgery aims for tumour-free surgical margins with the preservation of critical anatomical structures. However, a major challenge is reconstruction after resection to preserve function and cosmesis. Definitive radiotherapy is delivered either by external beams of radiation from a telecobalt machine or linear accelerator. The mainstay management of lymph node metastases is by radical neck dissection with or without post-operative radiotherapy. For patients with cancer of the larynx, very early tumours and cancer *in situ* can be managed with local surgery, while early invasive tumours can be managed with radiation therapy. More advanced tumours can be treated primarily with induction chemotherapy or chemoradiotherapy, reserving laryngectomy as a salvage procedure. Early nasopharynx cancer is treated with intensive radiotherapy while more advanced cancers should be treated with a combination of chemoradiotherapy and adjuvant chemotherapy.

Radiotherapy may also be used to sterilize microscopic residual cancer after surgery. In frail patients with accessible tumours (< 3 cm in size), brachytherapy over a 3-5 day period may be curative. Radiotherapy to the head and neck can lead to troublesome side-effects. Acute skin and mucosal inflammation and sometimes ulcerations, as well as superinfection with *Candida* (fungus), may make normal food intake impossible and necessitate use of a feeding tube. Later effects may include loss of taste, reduced and thick saliva production and a dry mouth [14]. Dental hygiene assessment and treatment prior to commencement of radiotherapy are extremely important.

Chemotherapy has not been demonstrated to elicit an overall improvement in survival, although combinations of cytotoxic drugs such as cisplatin, methotrexate, 5-fluorouracil and bleomycin can cause dramatic tumour reduction in 80-90% of cases. A combined approach, chemoradiotherapy, appears to improve overall survival [15].

The most important prognostic factors for oral cancer are regional lymph node involvement, size of the primary lesion, primary site of cancer within the oral cavity and age. The presence of a lymph node metastasis is the most important negative prognostic factor in squamous carcinoma of the mouth and pharynx. Aggressive histopathologic features include significant lymphovascular invasion, perineural infiltration or high grade. Overexpression of Bcl-2 is associated with improved survival in head and neck cancer patients undergoing radiation therapy, as well as with better local control and the absence of local lymph node involvement. Abnormalities of 11q13 are associated with a poor prognosis [12].

Overall population based five-year survival from oral cancer is mostly less than 50% (Fig. 5.95) [17]. Females, in general, have a higher
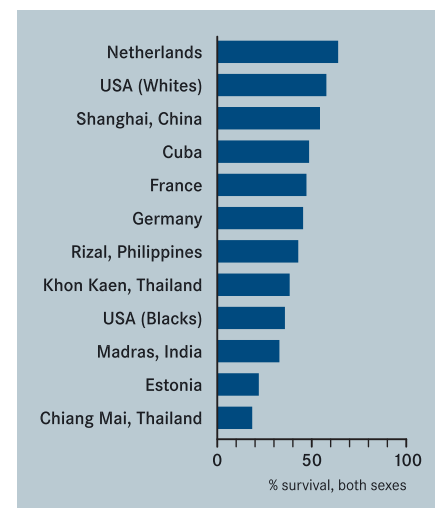

Fig. 5.95 Five-year relative survival after diagnosis of cancer of the oral cavity. USA data include both oral and pharyngeal cancers.
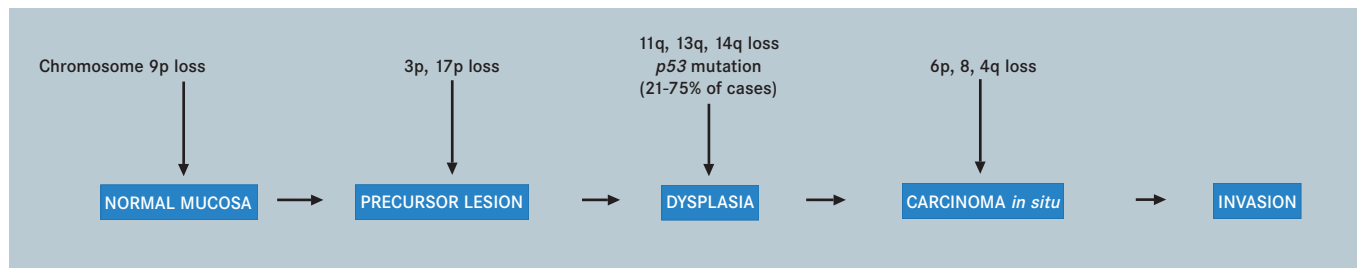
Fig. 5.96 Genetic alterations in squamous cell carcinoma of the head and neck. The accumulation and not necessarily the order of these genetic changes determines progression.

survival rate than males. There has been very little improvement in five-year survival from this cancer, or other head and neck cancers, over the last four decades [18]. Early-stage head and neck cancers have a good cure rate, but over 60% of patients present with advanced disease. Moreover, a significant percentage of patients with squamous cell carcinoma go on to develop a second primary tumour although initially cured. Patients may also face serious reductions in quality of life after definitive surgical therapy; despite improving rehabilitation and reconstructive surgery, residual cosmetic and functional debilities may be significant.

The overall relative survival of laryngeal cancer patients varies between 60 and 70% in Europe and North America, but is lower in developing countries. It is highly dependent on the sub-site of the disease which itself is dependent on the etiological factors involved. In countries with elevated alcohol consumption the prognosis is poorer because there are more tumours of the upper part of the larynx, which have a lower survival.

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WEBSITE

NCI Head and Neck Cancer Homepage:
http://www.cancer.gov/cancer_information/cancer_type/head_and_neck/

LYMPHOMA

SUMMARY

> Malignant lymphomas are classified as either Hodgkin disease or non-Hodgkin lymphoma.

> Hodgkin disease afflicts mainly children and the elderly in developing countries and young adults in more developed countries; 62,000 new cases are diagnosed annually.

> The incidence of malignant non-Hodgkin lymphomas is increasing worldwide; more than 280,000 new cases occur annually, predominantly in more developed countries.

> Burkitt lymphoma is a subtype of malignant B-cell lymphoma common in Africa in regions with endemic malaria. B-cell lymphomas may also be caused by immunosuppression. Both are commonly associated with the Epstein-Barr virus.

> Advances in chemotherapy have led to a five-year survival rate for Hodgkin disease of more than 70% and that for non-Hodgkin lymphomas has increased to 60-70%.

Definition

The term lymphoma covers a heterogeneous group of neoplasms of lymphoid tissue. Traditionally, lymphomas are categorized as either Hodgkin disease or non-Hodgkin lymphoma, these distinct entities having different patterns of behaviour and response to treatment. Within each of these two entities there is a range of diverse subtypes.

Epidemiology

Non-Hodgkin lymphomas are a very varied group of neoplasms. Excluding the types that generally manifest as leukaemias rather than single or multiple aggregates of cells, there are around 287,000 cases of non-Hodgkin lymphoma in the world
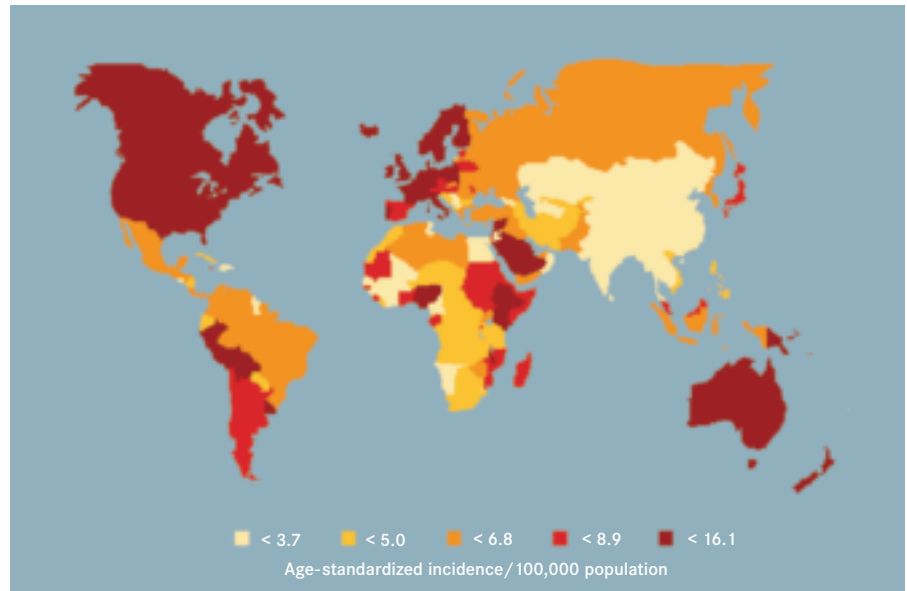

Fig. 5.97 Global incidence of non-Hodgkin lymphoma in men. The disease is most common in developed countries, although there are areas of moderate to high incidence in some Middle-Eastern countries and in parts of sub-Saharan Africa.

per year. More males than females are affected (17.1 cases per 100,000 males compared to 11.2 cases per 100,000 females in the USA) and incidence increases with age. Geographically, non-Hodgkin lymphoma is most common in developed countries (52% of the world total cases, and the seventh most common cancer in more developed countries), although in the developing world there are areas of moderate to high incidence in some Middle-Eastern countries (Saudi Arabia, Israel) and in parts of sub-Saharan Africa (Fig. 5.97). The latter is due to the high incidence of Burkitt lymphoma, an aggressive subtype of non-Hodgkin lymphoma, particularly in children in tropical Africa. Papua New Guinea also has high rates of Burkitt lymphoma.

The incidence rates of non-Hodgkin lymphoma have risen dramatically in the last 20 years, particularly in developed countries, including Western Europe, North America and Australia (Fig. 5.99). This may in part reflect better diagnosis, or

changing classification systems. However, these considerations together do not account for the extent of increase. Likewise, the fact that non-Hodgkin lymphoma is a complication of AIDS (occurring in up to 5-10% of AIDS cases in developed countries) does not completely account for the increasing trend. In contrast to incidence, mortality rates have, in general, been declining as a consequence of improvement in therapy.

Hodgkin disease comprises about 23% of malignant lymphomas worldwide (about 62,000 annual cases). There is a male predominance (sex ratio 1.6:1). In developing countries, Hodgkin disease (predominantly the mixed cellularity subtype) occurs mainly in children and in the elderly, while in developed countries there is a peak in young adults (mainly the nodular sclerosing subtype). The disease is rare in Eastern and South-Eastern Asian populations at any age (Fig. 5.100). The pattern of Hodgkin disease in black Americans more closely resembles that of white

Fig. 5.98 Non-Hodgkin lymphoma in the neck of a patient suffering from AIDS.

Fig. 5.99 Trends in incidence of non-Hodgkin lymphoma in the USA. Rates are increasing, as they are worldwide.

Americans than that of black Africans, suggesting that socioeconomic conditions may be more important than ethnicity in determining risk. In developed countries, incidence has fallen in the last 20 years [1]. Mortality rates are also decreasing, probably due to effective therapy.

Etiology

Non-Hodgkin lymphoma
Patients with HIV/AIDS (Box: *Tumours associated with HIV/AIDS*, p60), or who have received immunosuppressant therapy (*Immunosuppression*, p68), have a higher risk of developing non-Hodgkin lymphoma [2]. Viral infections such as HIV-1, HTLV-1 and EBV are also associated with non-Hodgkin lymphoma. Infection of the stomach with *Helicobacter pylori* is associated with gastric lymphoma. Agricultural work with possible exposure to pesticides (particularly chlorophenoxy herbicides) and occupational exposure to solvents or fertilizers have been implicated but have yet to be confirmed as causes of non-Hodgkin lymphoma.
There is an increased risk of non-Hodgkin lymphoma among persons with a family history of lymphoma or haematologic cancer [2].

Hodgkin disease
A subset of Hodgkin disease cases, particularly the mixed cellularity type, has been linked to the Epstein-Barr virus (EBV) [2]. Overall, around 45% of cases may be attributable to EBV. The presence of EBV in tumours seems also to be related to age and socioeconomic circumstances. EBV is involved in the etiology of Burkitt lymphoma,
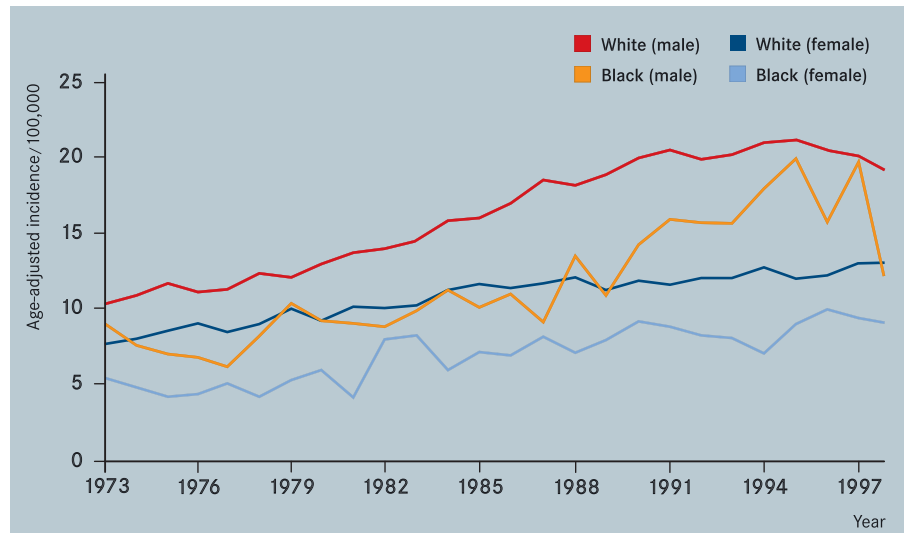
especially in cases in tropical Africa, where over 95% of tumours contain the virus. The proportion of EBV-positive tumours is much less in the sporadic cases of Hodgkin disease occurring in Europe and North America. The singular geographic distribution of Burkitt lymphoma is not explicable on the basis of EBV alone, however, since infection by the virus is ubiquitous. Suspicion has fallen upon intense malaria infection as predisposing to Burkitt lymphoma in the presence of EBV infection. Chronic exposure to wood or wood products has also been associated with increased risk. The risk of Hodgkin disease is also increased in patients with HIV infection.
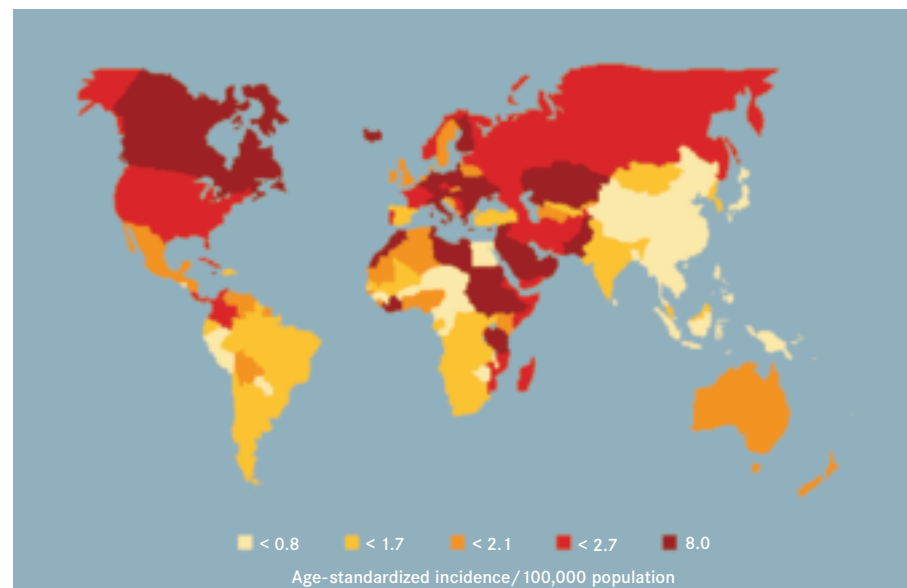

Fig. 5.100 Global incidence of Hodgkin disease in men. The disease is rare in Eastern and South-Eastern Asian populations.
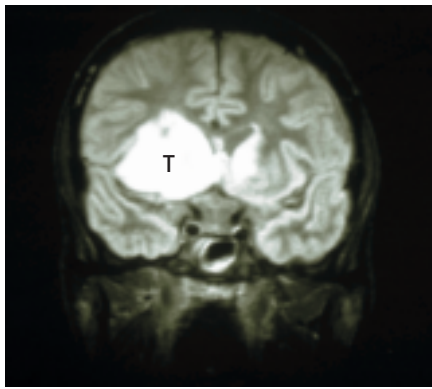
Fig. 5.101 Nuclear magnetic resonance imaging scan of the brain of an HIV-infected patient showing a large lymphoma (T) in the basal ganglia.
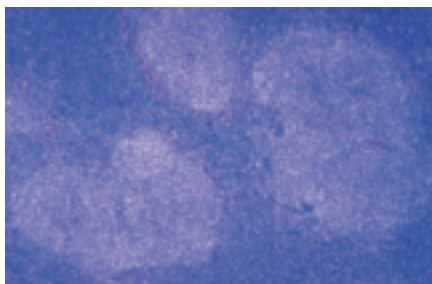

Fig. 5.102 Follicular non-Hodgkin lymphoma.

Detection

The most common presentation of non-Hodgkin lymphoma is painless swelling of the lymph nodes in the neck, armpit or groin. This may be associated with so called "B symptoms" of unexplained fever, night sweats and weight loss. Other related symptoms include fatigue, malaise, pruritus, or those related to organ involvement (e.g. indigestion caused by gastric lymphoma). Extranodal involvement is common. Diagnosis is dependent on obtaining a tissue biopsy, usually by excision of an enlarged node. Pathological review is crucial to identify the type of lymphoma.

Staging practice commonly involves full blood count, biochemical screen including tests of liver function and renal function, chest X-ray, CT scan of neck, chest, abdomen and pelvis, and bone marrow biopsy. In some instances, lumbar puncture may be required to assess central nervous system involvement, which can have important therapeutic implications. Hodgkin disease usually originates in lymph nodes (often in the neck), and only rarely spreads outside primary lymphoid tissues. Diagnosis requires a tissue biopsy, ideally a whole lymph node. Many of the staging techniques employed are the same as for non-Hodgkin lymphoma, and the Ann Arbor staging system is used to provide treatment planning information and aid response assessment.

Pathology and genetics

Lymphomas constitute a diverse range of diseases (Table 5.10). Advances in molecular biology, genetics and immunology have meant that there have been profound changes in the classification of neoplasms of lymphoid cells over the last 20 years. In the Revised European-American Lymphoma classification system, three broad categories are recognized: Hodgkin disease and T-cell and B-cell non-Hodgkin lymphomas. A WHO classification has recently been published [3]; prior to this the International Working Formulation (IWF) was the most widely used classification.

Non-Hodgkin lymphomas are derived from B or T lymphocytes. In Western countries, B-cell tumours are more common (about 75% of cases), whereas T-cell tumours are less common but are generally more biologically aggressive. T-cell tumours are relatively more common in East Asia. A follicular lymphoma is defined by the retention of the follicles within a lymph node (Fig. 5.102), whereas a diffuse lymphoma results from the infiltration of the node with effacement of the follicles by the malignant cells. The size of the malignant lymphocytes is also important.

In contrast, Hodgkin disease is characterized by the presence of multinucleate, giant so-called "Reed-Sternberg" cells, which may be rare in a particular biopsy specimen and the surrounding cell proliferation. The Revised European-American Lymphoma classification [4] also covers Hodgkin disease; four histological subtypes of Hodgkin disease are recognized: nodular sclerosing, mixed cellularity, lymphocyte predominance and lymphocyte depletion.

Many cytogenetic and molecular abnormalities in non-Hodgkin lymphoma, in particular Burkitt lymphoma, are caused by a translocation of the oncogene *C-MYC* from chromosome 8 to either the immunoglobulin heavy chain region on chromosome 14 or to one of the light chain loci on chromosomes 2 or 22 [5]. Technological innovations, such as microarrays, are revolutionizing diagnosis (Fig. 5.105).

Genetic abnormalities in Hodgkin disease are less frequently described, perhaps due to the paucity of malignant cells in the biopsy specimen.

Diagnosis	% of total cases
Diffuse large B-cell lymphoma	30.6
Follicular lymphoma	22.1
MALT lymphoma	7.6
Mature T-cell lymphomas (except ALCL)	7.6
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	6.7
Mantle cell lymphoma	6.0
Mediastinal large B-cell lymphoma	2.4
Anaplastic large cell lymphoma (ALCL)	2.4
Burkitt lymphoma	2.5
Nodal marginal zone lymphoma	1.8
Precursor T lymphoblastic	1.7
Lymphoplasmacytic lymphoma	1.2
Other types	7.4

Table 5.10 Frequency of various types of non-Hodgkin lymphoma.
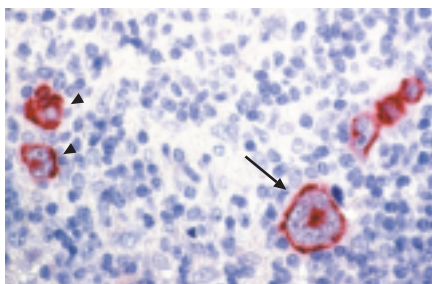
Fig. 5.103 Classical Hodgkin disease. Hodgkin (arrow) and Reed-Sternberg cells (arrowhead) infected by the Epstein-Barr virus strongly express the virus-encoded latent membrane protein LMP1.

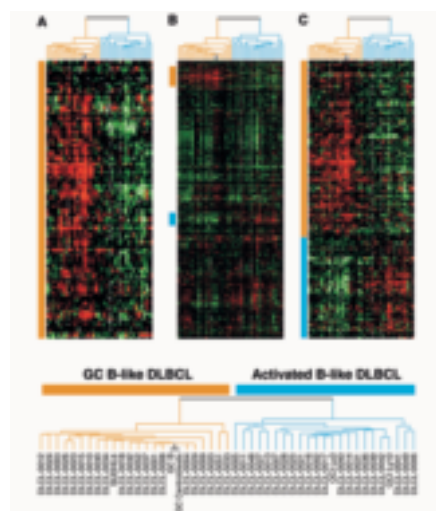Fig. 5.104 Burkitt lymphoma presenting as a large tumour of the jaw in an African child.

Fig. 5.105 Microarray technology can be used to identify two major patterns of gene expression among diffuse large B-cell lymphomas (DLBCL). One displays a germinal centre T-cell signature, the other an activated B-cell signature. The analysis is based on the expression of about 12,000 genes.

Management

The treatment of non-Hodgkin lymphomas depends on the pathological classification, the stage of the disease, the biological behaviour of the disease, the age of the patient and their general health [6,7]. In general, it is convenient to classify the pathological entities into indolent, aggressive or highly aggressive non-Hodgkin lymphomas, which parallels the IWF classification.

Indolent non-Hodgkin lymphomas

About two-thirds of indolent lymphomas in developed countries are follicular lymphomas and often present as advanced stage disease in patients over 50 years of age. This disease usually runs a prolonged course and is rarely cured (except in a few cases of early stage disease). The median survival is eight to ten years, and therapy is often palliative. Local radiotherapy is useful for early stage localized disease, and other options include alkylating agents, purine analogues, combination chemotherapy, interferon, monoclonal antibodies and high dose therapy with autologous stem cell support. Lymphoplasmacytoid lymphoma is often associated with a monoclonal paraprotein and, like small lymphocytic lymphoma/chronic lymphocytic leukaemia, will often respond to alkylating agent therapy. Marginal zone lymphomas can be divided into those at nodal sites (monocytoid B-cell lymphomas) and those at extra nodal sites, usually mucosal (gastrointestinal, lung, salivary gland etc.) when they are termed MALT (mucosa associated lymphoid tissue) lymphomas. Gastric MALT lymphomas are often associated with *H. pylori* infection and appropriate antibiotic treatment often results in resolution of the lymphoma, albeit over six to twelve months [8]. Splenic marginal zone lymphoma, often called splenic lymphoma with villous lymphocytes, presents with splenomegaly and usually responds to splenectomy.

Aggressive non-Hodgkin lymphomas

Diffuse large cell lymphoma is the most common of these types. Biologically these tumours are more aggressive than the indolent lymphomas, although remission and even cure may be obtained with appropriate therapy in a significant proportion of cases. The factors associated with prognosis in these patients are age, stage, performance status, the presence of extranodal disease, and lactic dehydrogenase levels, which can be summed to form the International Prognostic Index. Using this model, four risk groups can be identified with a predicted five-year survival of 73%, 51%, 43% and 26% when treated with conventional anthracycline based chemotherapy (e.g. cyclophosphamide, doxorubicin, vincristine, prednisone). Attempts to improve outcome with more aggressive chemo-

Histology	Translocations
Small cleaved cell, follicular	t(14;18)(q32;q21.3)
Small non-cleaved cell (Burkitt and non-Burkitt)	t(8;14)(q24;q32) t(2;8)(p12;q24) t(8;22)(q24;q11)
Centrocytic/mantle cell	t(11;14)(q13;q32)
Large cell, diffuse, B-cell	t(3;14)(q27;q32) t(3;22)(q27;q11) t(2;3)(p12;q27)
Small lymphocytic/extranodal (MALT)	t(11;18)(q21;q21.1)
Large cell, anaplastic	t(2;5)(p23;q35)

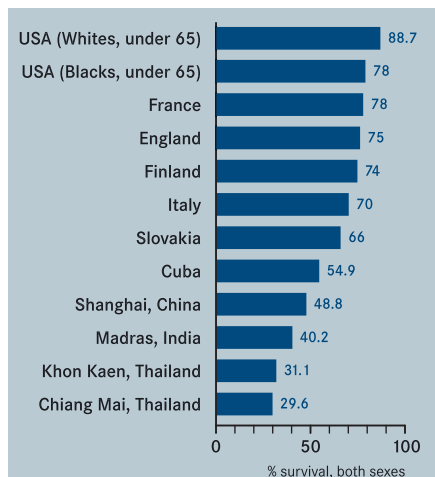Table 5.11 Some common chromosomal translocations found in non-Hodgkin lymphomas.

Fig. 5.106 Five-year relative survival rates after diagnosis of Hodgkin disease.
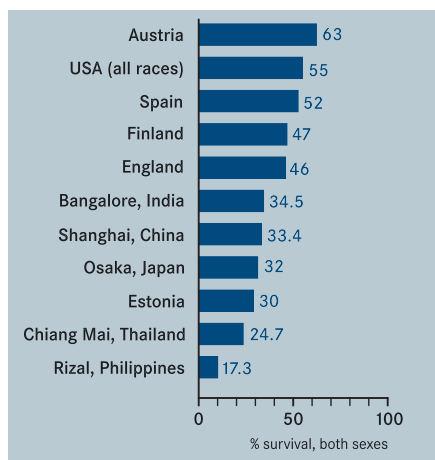

Fig. 5.107 Five-year relative survival rates after diagnosis of non-Hodgkin lymphoma.

therapy protocols, so-called "second and third generation regimens", have met with little success. However, the introduction of the International Prognostic Index may help to identify patients who will benefit from more aggressive strategies [9]. In patients who relapse after conventional therapy, and who still have "sensitive disease", high-dose chemotherapy with stem cell rescue appears to offer a reasonable salvage option.

Hodgkin disease
In contrast to non-Hodgkin lymphomas, the management of Hodgkin disease is usually dictated by the stage of disease rather than the histology [10,11]. Most centres would use radiotherapy for early stage (IA or IIA) disease, although there is a trend towards considering limited chemotherapy as an option. All other stages should have chemotherapy, and the traditional "gold standard" MOPP (mustine, vincristine, procarbazine and prednisone) therapy has been superseded by ABVD (adriamycin [doxorubicin], bleomycin, vinblastine and dacarbazine) which appears to be as efficacious without the adverse effects (particularly related to fertility and the development of second malignancies). The German Hodgkin Disease Study Group has proposed a prognostic model for advanced stage disease, and has identified seven factors which influence outcome. These are age, sex, histology, B symptoms, number of involved sites, bulk of disease and erythrocyte sedimentation rate. Using such models it may be possible to identify poor prognosis patients who will benefit from more aggressive high-dose therapies, such as Stanford V (doxorubicin, vinblastine, mustard, bleomycin, vincristine, etoposide and prednisone) or BEACOPP (bleomycin, etoposide, adriamycin [doxorubicin], cyclophosphamide, oncovin [vincristine], procarbazine and prednisone) from the outset (*Medical oncology*, p281).

Survival for both Hodgkin disease and non-Hodgkin lymphomas has improved markedly with time, in response to the development of more effective chemotherapy and bone marrow transplantation. Five-year survival after diagnosis of non-Hodgkin lymphoma patients in most developed countries is more than 50%, but only 17-35% in developing countries (Fig. 5.107). Currently, survival of Hodgkin disease patients is related to extent of disease at diagnosis; overall, at five years it is between 70% and 90% in North America and Europe, but only 30-55% in developing countries (Fig. 5.106).

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LEUKAEMIA

SUMMARY

> Leukaemia is the eleventh most common cancer worldwide with more than 250,000 new cases each year. It typicallyresults from malignant transformation of white blood cells or their precursors. Subtypes are identified on the basis of the cell of origin (lymphocytic or myeloid, etc.) and clinical course (acute or chronic).

> The etiology of leukaemia is largely unknown, although a small proportion of cases is attributable to treatment with anticancer drugs or exposure to ionizing radiation. The genetic characteristics of many leukaemias have been elucidated.

> Treatment of acute leukaemia has made muchg progress and helped to establish general principles of cancer chemotherapy and management.

> Survival varies greatly according to type, with acute lymphoblastic leukaemia patients having a five-year survival rate of up to 70%, whilst for those with acute myeloid leukaemia it is only 20-30%.

Fig. 5.108 Global incidence of leukaemia in women.

Definition

Leukaemias involve clonal, neoplastic proliferation of immature cells, or blasts, of the haematopoietic system. Principal subtypes are identified on the basis of malignancy involving either lymphoid (B-cells and T-cells) or myeloid (i.e. granulocytic, erythroid and megakaryocytic) cells, and upon whether disease is acute or chronic in onset [1].

Epidemiology

Leukaemias comprise about 3% of all incident cancers worldwide, with about 257,000 new cases occurring annually. Incidence rates for all types taken together vary from about 1 to 12 per 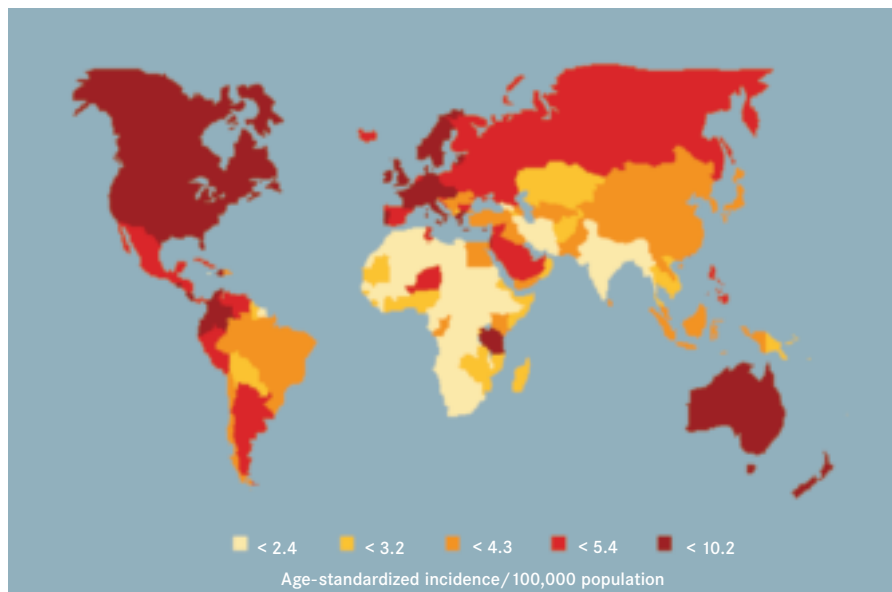100,000 population. A relatively high incidence is evident in the USA, Canada, Western Europe, Australia and New Zealand, whilst rates are generally low in most African and Asian countries with rates less than half those in the former group (Fig. 5.108). The trends in overall incidence of leukaemia have generally been stable or slowly increasing. However, a substantial reduction in death rates from leukaemias, particularly in childhood, have been observed since the 1960s, thanks to advances in treatment and consequent improvement in survival.

Leukaemia has a peak in incidence in the first four years of life, which is predominantly due to acute lymphoblastic leukaemia (ALL), the most common paediatric malignancy, accounting for nearly 25% of all such disease. After infancy, there is a steep decline in rates of leukaemia with age, lowest incidence being at age 15 to 25, after which there is an exponential rise up to age 85 (Fig. 5.110). The frequency of leukaemia per 100,000 individuals at risk at age 85 is more than 300 times that for those in the second decade of life.

The overall incidence of acute leukaemia is 4 cases per 100,000 population, the usual form of the disease in adults being acute myeloid leukaemia (AML) accounting for 70% of all cases. The more differentiated, or chronic forms of leukaemia, are predominantly adult diseases, rarely occurring below the age of 30, then increasing progressively in incidence with age. Chronic myelogenous leukaemia (CML) accounts for 15-20% of all cases of leukaemia, with a worldwide incidence of 1-1.5 cases per 100,000 population. For patients over 50, chronic lymphocytic leukaemia (CLL) is the dominant type of leukaemia. All types of leukaemia combined cause some 195,000 deaths worldwide.

Etiology

The cause of most leukaemias is not known. A range of risk factors has been predominantly, although not exclusively, associated with particular leukaemia subtypes. Ionizing radiation (nuclear bombs, medical procedures, [e.g. 2, 3]) and occupational exposure to benzene are associated with acute myeloid leukaemia.

Fig. 5.109 The immediate aftermath of a nuclear explosion. An increased incidence of leukaemia and some other cancer types occurred amongst the survivors of the bombing of Hiroshima and Nagasaki.

Fig. 5.110 Age-specific incidence rates in the USA of leukaemia overall and of different subtypes. AML = acute myeloid leukaemia, ALL = acute lymphoblastic leukaemia, CLL = chronic lymphocytic leukaemia, CML = chronic myelogenous leukaemia. Note the high incidence of ALL in children.

Leukaemia (mainly acute myeloid) may occur in a small proportion of cancer patients treated with chloroambucil, cyclophosphamide, melphalan, thiotepa, treosulphan or etoposide, as well as certain combination chemotherapy (*Medicinal drugs*, p48). Leukaemia has followed induction of aplastic anaemia by the antibiotic, chloramphenicol. Certain risk factors, such as Down's syndrome, have been identified for childhood leukaemia, but generally the causes of the disease are not known. Some studies have shown a risk of childhood leukaemia with exposure to high level residential extremely low frequency electromagnetic fields, but causality has not been established [4].

Infection with the virus HTLV-I has been established as a cause of leukaemia. This virus is responsible for adult T-cell leukaemia, a disease mainly observed in tropical countries and Japan, and rarely in the USA and Europe. In experimental animals, particularly in mice, there are many retroviruses which can cause a variety of leukaemias, but such retroviruses have not been identified in humans.

Detection

In the case of the myeloid leukaemias, the primary manifestations result from suppression of normal haematopoiesis. This causes anaemia, leading to weakness, leukopenia (decreased numbers of white blood cells) resulting in an increased frequency of infection, and thrombo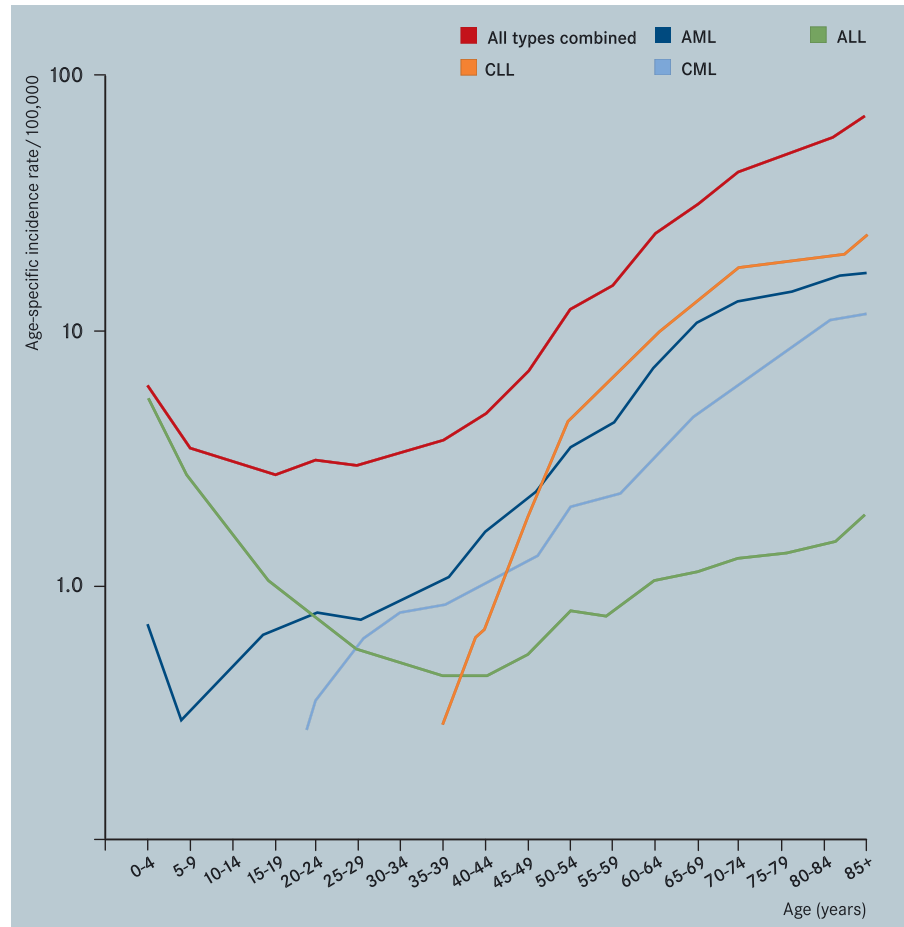cytopenia (decreased numbers of platelets) resulting in increased risk of haemorrhage. Patients with chronic myelogenous leukaemia, usually adults aged 30-50, present with slow onset of symptoms of anaemia, weight loss and massive enlargement of the spleen.

In the case of lymphoid malignancies, the primary effect is on the host immune response, with an increased susceptibility to infection and, in the advanced stages, interference with bone marrow function. Children with acute lymphoblastic leukaemia (or young adults with acute myeloid leukaemia) may present with anaemia, features of infection and bleeding, which are of rapid onset. Enlargement of the liver and spleen is common. Patients with acute lymphoblastic leukaemia additionally present with bone and joint pain and multiple lymph node enlargement (lymphadenopathy). Chronic lymphocytic leukaemia presents with multiple lymph node enlargement, with or without splenic enlargement. As the disease progresses, anaemia sets in slowly. For leukaemia generally, diagnosis may be suspected from examination of peripheral blood and is confirmed by bone marrow examination.

Pathology and genetics

Leukaemias are clonal neoplastic proliferations of immature haematopoietic cells characterized by aberrant or arrested differentiation. Leukaemic cells rapid-
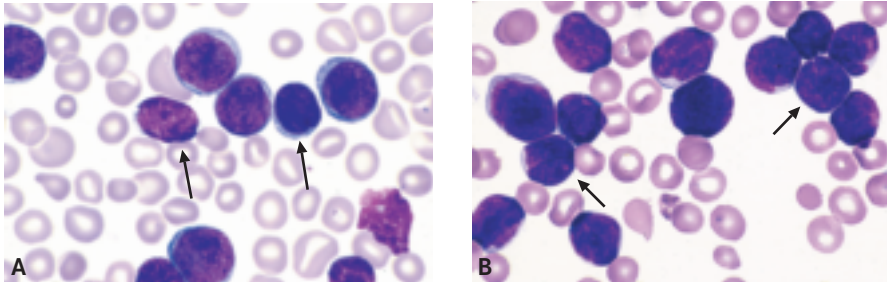
Fig. 5.111 (A) Bone marrow smear from a patient with acute lymphoblastic leukaemia. (B) Precursor B lymphoblastic leukaemia. This bone marrow smear shows several lymphoblasts with a high nuclear cytoplasmic ratio and variably condensed nuclear chromatin.

ly accumulate in the bone marrow, ultimately replacing most of the normal cells and circulate in the peripheral blood. As already noted, leukaemias are categorized in relation to clinical course and cell lineage. In addition, reference may be made to the morphology, degree of differentiation, immuno-phenotype and genetic character of the malignant cell population [5].

Acute lymphoblastic leukaemia (Fig. 5.111 A) is characterized by lymphoblasts, most often of B-cell phenotype (about 80% of both childhood and adult disease), and distinguished from lymphomas which involve more mature lymphoid cells and primarily inhabit lymph nodes and spleen. Precursor B-lineage blasts (Fig. 5.111B) exhibit a range of cytogenetic abnormalities. The t(9;22) translocation, which results in fusion of the "breakpoint cluster region" BCR on chromosome 22 and the cytoplasmic tyrosine kinase ABL on chromosome 9, is associated with poor prognosis. B-lineage blasts express surface antigens such as CD10, CD19 and CD22 [6]. Precursor

T-cell phenotypes, expressing CD2, CD3, CD5 and CD7 surface antigens, make up 15-20% of acute lymphoblastic leukaemia cases.

Acute myeloid leukaemia (Fig. 5.113) is a clonal expansion of myeloid blasts in bone marrow, blood or other tissue [5]. The disease is heterogeneous and consists of several subtypes, which can be identified by karyotype [7]. Approximately 20% of patients have favourable cytogenetic abnormalities, including t(8;21), inv(16) and t(15;17). These types are uniformly distributed across age groups, suggesting a distinct etiologic agent. Approximately 30% (predominantly patients over the age of 50, with a progressive increase in incidence with age) have unfavourable cytogenetic abnormalities, which include deletions of the long arm of chromosome 5 or 7 or trisomy of chromosome 8. Approximately half have diploid cytogenetics and an intermediate prognosis. A significant fraction of the favourable cytogenetic group and a small fraction of the diploid group can be cured with combination chemotherapy. One subtype, acute promyelocytic leukaemia, is characterized by t(15;17) (Fig. 5.114, 5.116). The break point on chromosome 17 occurs within the gene for an all-trans-retinoic acid receptor (RARα) and generates the fusion gene PML-RARα on the derivative chromosome 15 [8].

Chronic myelogenous leukaemia (Fig. 5.117) originates in an abnormal pluripotent bone marrow stem cell [5,9]. The disease has a cytogenetic hallmark, the Philadelphia chromosome, namely t(9;22) (Fig. 5.115). This translocation relocates the C-ABL proto-oncogene from chromosome 9 to the breakpoint cluster region on chromosome 22 to form a new hybrid BCR-ABL oncogene. The BCR-ABL transcript is present in over 95% of chronic myelogenous leukaemia cases, and encodes a novel tyrosine kinase that is involved in pathogenesis, possibly by perturbing apoptosis.

Chronic lymphocytic leukaemia is now recognized as being the same disease entity as small cell lymphoma, being a neoplasm of monomorphic small, round B-lymphocytes in the peripheral blood,
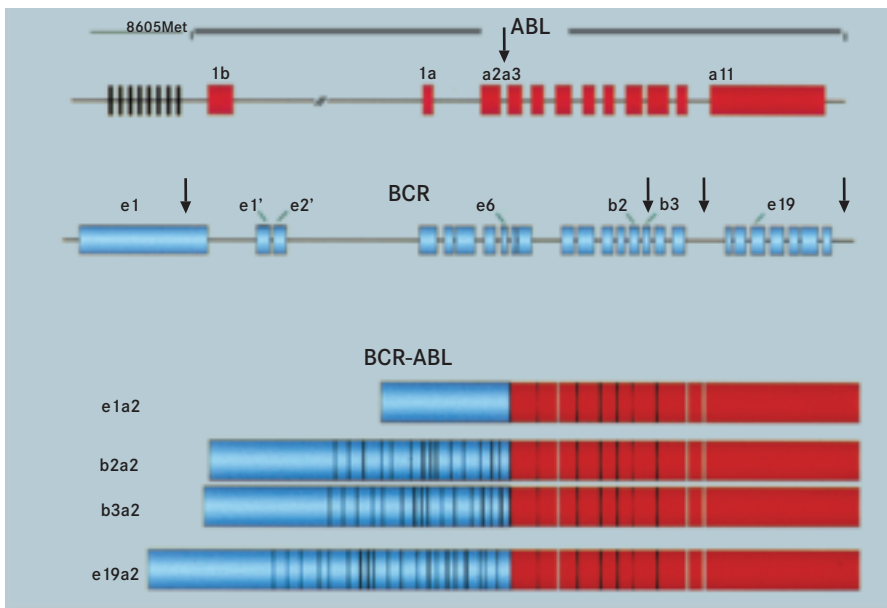

Fig. 5.112 Schematic representation of the disruption of the ABL and BCR genes in the t(9;22)(q34;21) chromosomal abnormality found in chronic myeloid leukaemia, which results in the formation of oncogenic BCR-ABL fusion genes. Segments of DNA which are transcribed to form the protein (exons) are labelled a, b and e. Arrows mark the breakage points.
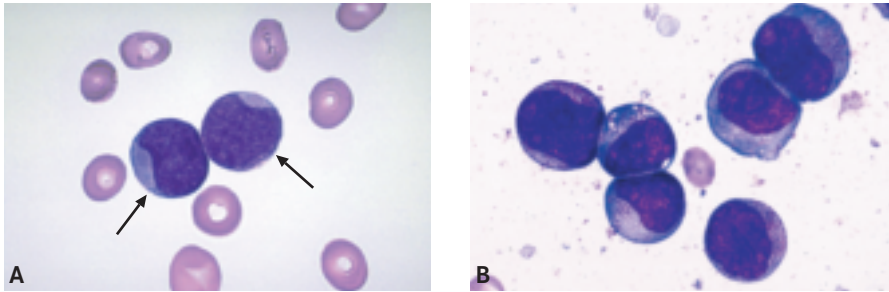
Fig. 5.113 Acute myeloid leukaemia; agranular myeloblasts **(A)** and granulated myeloblasts **(B)**.
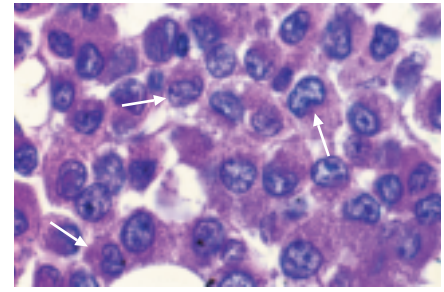

Fig. 5.114 A bone marrow biopsy of acute promyelocytic leukaemia. Abnormal promyelocytes have abundant hypergranulated cytoplasm. The nuclei are generally round to oval, several being irregular and invaginated.

bone marrow and lymph nodes, admixed with prolymphocytes and paraimmunoblasts, usually expressing CD5 and CD23 surface antigen [5]. Chronic lymphocytic leukaemia [10] is a heterogeneous disease which can occur in an indolent form with very little progression, whilst at the other extreme it may present with severe bone marrow failure and a poor prognosis.

Management

Remarkable progress in the understanding and treatment of leukaemia has been made in the past century [11]. In the first instance, this generalization refers specifically to paediatric disease. Prior to 1960, leukaemia was the leading cause of death from malignancy in children under 15; currently, more than 80% of children with acute lymphoblastic leukaemia can be cured with chemotherapy [12]. Treatment involves induction of remission with combinations of agents (such as vincristine, daunorubicin, cytarabine [cytosine arabinoside], L-asparaginase, 6-thioguanine, and steroids) followed by consolidation, maintenance and post-remission intensification therapy to eradicate residual leukaemic blast cells, aiming at cure. Intensive supportive care throughout treatment is of major importance. Prophylactic treatment with intrathecal methotrexate injections, with or without craniospinal irradiation, is mandatory in the management of acute lymphoblastic leukaemia to prevent possible involvement of or relapse in the central nervous system. The use of radiotherapy is limited because of the potential long-term side-effects, particularly effects on the growth of the young child and the risk of second malignancies. The adult form of acute lymphoblastic leukaemia is also susceptible to therapy and can be cured, (although not as readily as childhood leukaemia), with intensive combination therapy [13].

For acute leukaemia in adults, the initial aim of management is to stabilize the patient with supportive measures to counteract bone marrow failure which leads to anaemia, neutropenia and thrombocytopenia. Most patients with leukaemia who die in the first three weeks of diagno-
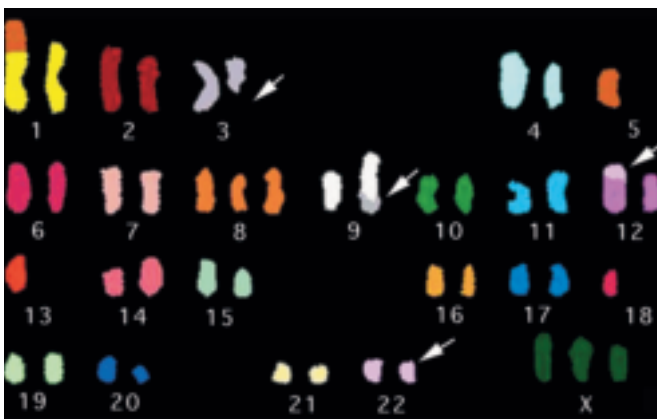

Fig. 5.115 Spectral karyotyping of a chronic myeloid leukaemia case reveals a variant Philadelphia chromosome involving translocations between chromosomes 3, 9, 12 and 22. Secondary changes involving chromosomes 1, 5, 8, 18 and X are also seen, indicating advanced disease.
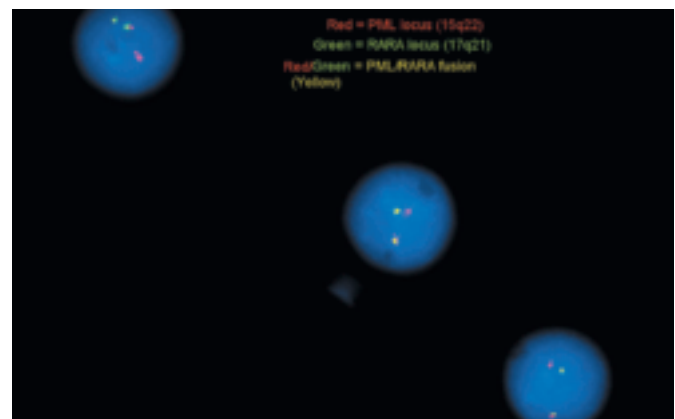

Fig. 5.116 Acute promyelocytic leukaemia cells with t(15;17)(q22;q12) translocation. Fluorescence *in situ* hybridization with probes for PML (red) and RARα (green) demonstrates the presence of a PML/RARα fusion protein (overlapping of red and green = yellow signal) resulting from the breakage and fusion of these chromosome bands.

THE MOLECULAR DETECTION OF MINIMAL RESIDUAL DISEASE

The accurate identification of submicroscopic numbers of residual cancer cells has important clinical implications for many malignancies. Treatment efficacy is frequently monitored by the disappearance of tumour cells from the blood or bone marrow, and while microscopic examination of marrow is extremely valuable, it is a relatively insensitive tool for the detection of this "minimal residual disease". Much effort has therefore been directed towards the development of sensitive and specific molecular assays of minimal residual disease with the main molecular strategy involving the use of the polymerase chain reaction (PCR) technique. Since its inception in 1985, this technique has been widely utilized as a means of amplifying (i.e. repeatedly copying) target DNA sequences up to a million-fold with great specificity, due to the use of oligonucleotide primers unique to the sequence of interest (Saiki RK et al., *Science,* 230: 1350-54, 1985). Numerous studies have reported the use of PCR-based techniques for detecting minimal residual disease in a range of cancers including leukaemia, lymphoma, breast cancer, prostate cancer and melanoma. Detection limits of one cancer cell amongst 10^4-10^6 normal cells can routinely be achieved, a level of sensitivity that is some 3 to 5 orders of magnitude more sensitive than conventional techniques. PCR can, therefore, serve as an ultrasensitive tool for accurately identifying small numbers of cancer cells in patient samples.

The potential clinical utility of minimal residual disease detection for both haematopoietic malignancies and solid tumours has been demonstrated in a range of studies. For example, there is now strong evidence that the level of minimal residual disease measured in the first few months of therapy in children undergoing treatment for acute lymphoblastic leukaemia is highly prognostic of outcome (Cave H et al., *New Engl J Med,* 339: 591-8, 1998; van Dongen JJM et al., *Lancet*, 352:1731-8, 1998). These studies have utilized clone-specific rearrangements of antigen receptor genes as the targets for PCR amplification of genomic DNA. Other studies, particularly those involving solid tumours, have relied on reverse transcriptase (RT-PCR) amplification of cancer-specific messenger RNA as an indicator of the presence of residual disease. While these RT-PCR techniques offer valuable clinical information, especially in tumour staging, there is currently enormous variability when comparing inter-laboratory assays. Such ultrasensitive methods can be plagued by false positivity of normal bone marrow and peripheral blood samples, particularly since it has been shown that by using RT-PCR it is possible to detect the expression of otherwise tissue-specific genes in any cell type. This process has been termed "illegitimate" transcription (Chelly J et al., *Proc Natl Acad Sci USA*, 86: 2617-21, 1989) and in order to avoid this it may be necessary to employ multiple markers for use in residual disease testing.

The molecular detection of minimal residual disease undoubtedly offers great potential as an aid in the management of cancer patients. However, there is also an urgent need to develop appropriate treatment strategies for use in conjunction with this new tool. It is at present unknown whether patients in whom persistent minimal residual disease is detected will benefit from adjuvant therapy, although a number of clinical trials have begun in order to address this question. Critical to their success will be the use of uniform and standardized minimal residual disease methods that provide accurate and reproducible results. The use of multiple molecular minimal residual disease markers and the development of "real-time" PCR assays (e.g. Kwan E et al., *Brit J Haem,* 109: 430-34, 2000) may be particularly helpful in this regard.
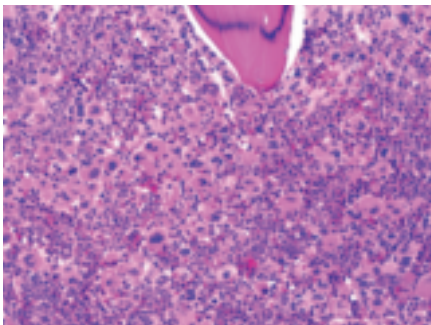

Fig. 5.117 A biopsy section from a patient with chronic myelogenous leukaemia, myeloid blast phase. Sheets of abnormal megakaryocytes, including micromegakaryocytes, are illustrated. Blasts infiltrate between the abnormal megakaryocytes.

sis die of infection or, less commonly, bleeding. Large gains in survival in acute myeloid leukaemia have come with the introduction of improved supportive care and combination chemotherapy. Effective drugs include cytarabine, anthracyclines, etoposide, mitoxantrone, amsacrine, 6-thioguanine and 5-azacytidine. Intensive therapy is applied until a complete remission is achieved with <5% blasts in the marrow. Typically, 50-70% of patients achieve complete remission. Bone marrow transplantation from an HLA-matched donor is one form of therapy for the late intensification of remission in younger patients with acute myeloid leukaemia.

Retinoic acid derivatives, particularly *all-trans*-retinoic acid, given by mouth can induce haematologic remissions of acute promyelocytic leukaemia without significant myelosuppression, although this therapy itself is not curative.
Treatment is essentially palliative in chronic leukaemias. The major risk to patients with chronic myelogenous leukaemia is transformation to an acute phase, which resembles acute leukaemia and is referred to as the blastic phase of the disease. This development is highly malignant and refractory to conventional treatment and results in a short survival. The anti-tyrosine kinase compound "Gleevec", or

Fig. 5.118 Five-year relative survival rates after diagnosis of leukaemia.

ST-571, α-interferon and arabinosyl cytosine, a chemotherapeutic agent, can produce complete cytogenetic remissions, prevention of blastic transformation and significant prolongation of survival, with a small fraction of patients being cured. However, the development of resistance to ST-571 may cause patients to relapse within a few months [14]. Without treatment, the life span for the average individual with chronic lymphocytic leukaemia is under five years from diagnosis. The treatment for this disease historically was with alkylating agents. Recently the purine antimetabolite, fludarabine, has substantially increased the frequency and the quality of response to chemotherapy. A new monoclonal antibody directed against the T-cell antigen, CD52 ("CAMPATH"), has been found to be highly effective in this disease. At the present time, combinations of antimetabolite, alkylating agents and monoclonal antibody in various combinations and sequences are being aggressively investigated and the prognosis for patients in this category of disease has substantially improved.

Generally, 60-70% of patients with acute lymphoblastic leukaemia, and 20-30% of patients with acute myeloid leukaemia (Fig. 5.118) survive in excess of five years. Approximately 30-50% of the patients diagnosed with chronic leukaemias survive five years. Survival is much poorer in developing countries (generally <20%) due to the cost and lack of access to these complex therapeutic regimes.

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WEBSITE

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PANCREATIC CANCER

SUMMARY

> Pancreatic cancer is the 14th most common cancer worldwide, with approximately 216,000 new cases per year. Highest incidence rates occur in more developed countries.

> In countries with high smoking prevalence, more than 40% of cases is attributable to tobacco consumption. Familial risk, often involving hereditary pancreatitis, is evident in up to 10% of cases.

> No effective early diagnostic test or population-based screening procedure is available.

> *KRAS* and *p53* gene mutations are implicated in the development of the most common type, ductal adenocarcinoma.

> Five-year survival rates are poor (less than 5%) and the vast majority of pancreatic cancer patients die within a year of clinical diagnosis.

| < 2.1 | < 5.6 | < 9 | < 1.5 | < 98.9 |

Age-standardized incidence/100,000 population

Fig. 5.119 Global burden of pancreatic cancer in women. Incidence rates are generally high in the Americas, Europe and Australia.

Definition

Most (90%) pancreatic tumours are adenocarcinomas arising from the ductal epithelium of the exocrine pancreas. Some 70% of these tumours develop in the head of the pancreas. Endocrine tumours of the pancreas, which are rare, arise from the islets of Langerhans.

Epidemiology

Pancreatic cancer is the 14th most common cancer worldwide, with more than 216,000 new cases occurring each year. Groups with the highest incidence include black male Americans, New Zealand Maoris, Korean Americans and native female Hawaiians, as well as the male population of Kazakhstan. The lowest rates are in Ahmedabad Indians and in the populations of some Africa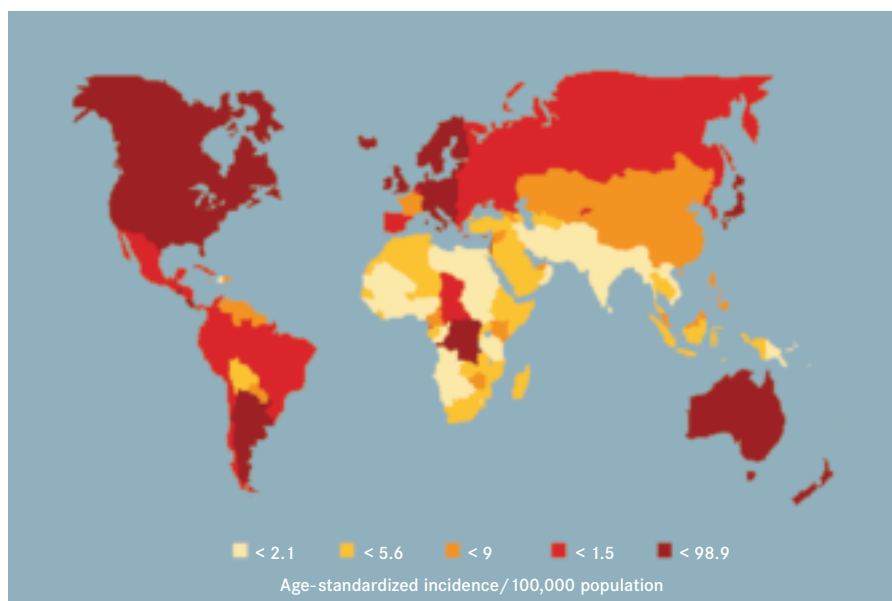n countries such as Tanzania and Guinea, and in those of Papua New Guinea and Sri Lanka [1] (Fig. 5.119). In the developed world, incidence has risen three-fold since the 1920s, stabilizing in the late 1970s. Pancreatic cancer is significantly more common in younger men than in younger women, the sex ratio varying from between 1.25-1.75:1 [2]. However, the gender bias decreases with increasing age. Prognosis is very poor and pancreatic cancer causes some 213,000 deaths each year. In the USA, cancer of the pancreas is now the fourth leading cause of cancer-related death in both men and women.

Etiology

About 30% of cases of pancreatic cancer are attributable to smoking. Cigarette smokers develop this disease two to three times more often than non-smokers. A number of dietary factors have been putatively connected with pancreatic cancer, including a diet low in fibre and high in meat and fat, and a diet rich in the heterocyclic amines present in cooked meat and fish. Smoking and diet are believed to account for much of the increased incidence observed since the 1920s. Coffee consumption was once thought to be a risk factor, but recent studies have not established significant associations.

Working in mines, metalworks, sawmills, chemical plants, coke plants, rubber factories, and the petrochemical industry have been variously indicated as risk factors, as has exposure to solvents, naphthylamine, benzidine, and polychlorinated biphenyl used in transformers. Other risk factors include chronic and hereditary pancreatitis, diabetes (although the significance of the latter is much weaker if cases of recent onset are excluded) and cirrhosis. The sex ratio of pancreatic cancer incidence has suggested a role for sex hormones in disease development [3].

Detection

The diagnosis of pancreatic cancer is rarely made at an early stage and the most frequently recognized clinical symptoms are usually portents of advanced dis-
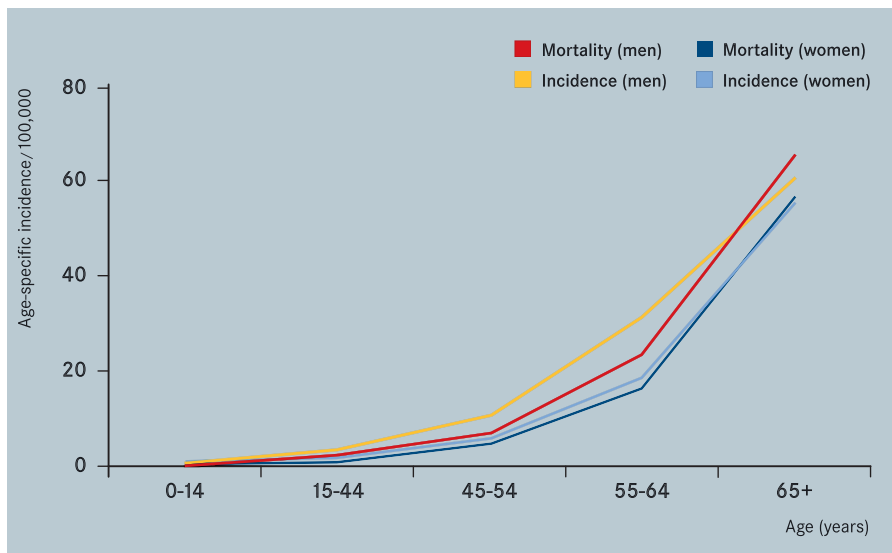
Fig. 5.120 Age-specific incidence and mortality of pancreatic cancer in men and women in North America. The small differences between incidence and mortality reflect the very poor prognosis of this disease. Men are somewhat more frequently affected than women.

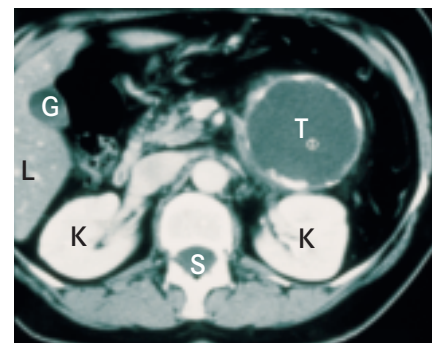Fig. 5.121 Cigarette smoking is one of the main risk factors for pancreatic cancer.

Fig. 5.122 A CT image of a mucinous cystic neoplasm in the pancreas. The thick wall shows focal calcification. T = tumour, K = kidney, L = liver, S = spinal cord, G = gallbladder.
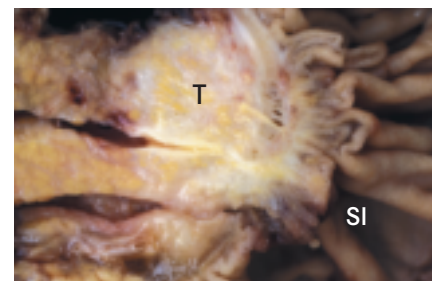

Fig. 5.123 Surgical specimen of a pancreatic ductal adenocarcinoma (T) in the head of the pancreas. SI = small intestine.

ease. These include unexplained weight loss, nausea, diarrhoea, weakness, jaundice (caused by compression of the intrapancreatic common bile duct) and upper abdominal and back pain. Mature onset diabetes in the absence of a family history may also indicate the possibility of pancreatic cancer. Insulin antagonism by tumour-produced factors (islet amyloid peptide, glucagon and somatostatin) is believed to be the cause [4]. Whilst 85% of patients have systemic disease or locally unresectable tumours on clinical evaluation, some 25% have symptoms compatible with upper abdominal disease up to six months prior to diagnosis and 15% of patients seek medical attention more than six months prior to diagnosis [5].

Ultrasonography is the initial diagnostic imaging system currently employed, although visualization of the body and tail of the pancreas is often unsatisfactory due to the presence of intestinal gas. Computed tomography (CT) scanning allows clearer imaging of the tail and body and can detect lesions of >1 cm with accuracy, as well as secondary signs of pancreatic cancer, such as dilation of common bile and main pancreatic ducts, invasion of surrounding structures, liver secondaries, lymphadenopathy and ascites (Fig. 5.122).

Cytological or histological confirmation is obtained from samples taken during endoscopic retrograde cholangiopancreatography, or by fine needle aspiration and core biopsy under radiological guidance. However, it is often difficult to obtain histological proof for small lesions, which have the best potential for curative surgery. Patients who are candidates for surgery undergo ultrasound and laparoscopy, which identify those with small peritoneal and liver nodules below the resolution of current imaging.

Pathology and genetics

The first stage of neoplasia (Fig. 5.124), flat hyperplasia, entails the columnarization of the ductal epithelium. It is estimated that as many as half the normal elderly population may exhibit flat hyperplasia [6]. This may advance to papillary hyperplasia, the presence of a crowded mucosa with a folded structure, which may possess varying degrees of cellular and nuclear abnormalities. True carcinoma is characterized by invasion of the ductal wall and a desmoplastic response, i.e. acollagenous, inflammatory reaction, such that the tumour may comprise less than 25% cancer cells. The major histological types include benign microcystic serous adeno-

ma, tumours of uncertain biological behaviour, including mucinous cystic tumour and solid cystic tumour, as well as malignant forms, such as adenocarcinoma, microcystic serous adenocarcinoma and mucinous cystadenocarcinoma.
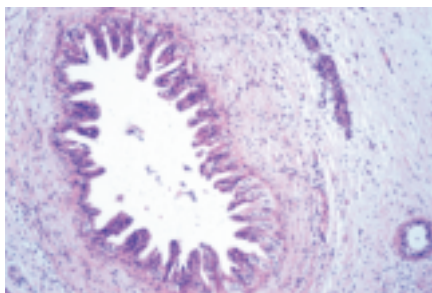
Fig. 5.124 Pancreatic duct showing high-grade intraepithelial neoplasia.
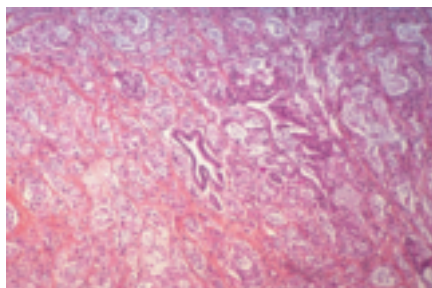

Fig. 5.125 Well-differentiated, mucus-secreting invasive ductal adenocarcinoma of the pancreas.

Hereditary conditions
Around 10% of cases of pancreatic cancer exhibit some degree of familial risk, this fraction being the highest for any human organ site [6]. In this context, germline mutations have been identified in a number of oncogenes and tumour suppressors, including *BRCA2*, (predisposing to breast and pancreatic carcinoma) and p16^INK4 (predisposing to melanoma and pancreatic cancer) (Table 5.13). The *STK11/LKB1* gene is mutated in Peutz-Jeghers syndrome patients, this group being predisposed to pancreatic cancer [7]. Sufferers from hereditary pancreatitis experience attacks of acute pancreatitis from an early age and face a 40% risk of cancer by age 70. Most families appear to possess one of two mutations in the cationic trypsinogen gene (chromosome 7q35) [8] which cause the production of a mutant protein. Consequently, associated enzymatic activity is not inactivated and is hypothesized to contribute to autodigestion of the pancreas and pancreatitis; cancer may then be a consequence of the prolonged inflammatory microenvironment in the pancreas. Other conditions which carry increased susceptibility to pancreatic cancer include intraductal papillary mucinous tumour, familial adenomatous polyposis, familial atypical multiple mole melanoma syndrome, cystic fibrosis, heritable nonpolyposis colon cancer and Li-Fraumeni syndrome [9].

Sporadic genetic alterations
Mutations of the *KRAS* oncogene, most frequently of codon 12, occur in 95% of sporadic pancreatic tumours and may represent an early molecular event in pancreatic carcinogenesis; they may also be present in some benign lesions [6]. Alterations in tumour suppressor genes such as *p53*, p16^INK4, *DCC* and *DPC4/SMAD4* have also been detailed, as has overexpression of some growth factors e.g. EGF, TGFα, TGFβ1-3, αFGF and their receptors [10, 11]. Mutation of the gene encoding c-erbB2 is associated with late stage pancreatic adenocarcinoma and that encoding c-erbB3 with shorter postoperative survival. (Table 5.12) [12].

Management
Currently, surgery offers the patient the only chance of cure. However, treatment can improve quality of life by controlling the symptoms and complications of this disease. Pancreaticoduodenectomy, the "Whipple procedure", involves the resection of all of the duodenum with a short section of the jejunum, the pancreatic head, cholecystectomy and excision of the common bile duct and a distal gastrectomy followed by reconstruction.

Gene	Chromosome	Mechanism of alteration	% of cancers
Oncogenes			
KRAS	12p	Point mutation	> 90
MYB, AKT2, AIB1	6q, 19q, 20q	Amplification[1]	10-20
ERBB2 (HER/2-neu)	17q	Overexpression	70
Tumour suppressor genes			
p16^INK4A	9p	Homozygous deletion	40
		Loss of heterozygosity and intragenic mutation	40
		Promoter hypermethylation	15
p53	17p	Loss of heterozygosity and intragenic mutation	50-70
DPC4	18q	Homozygous deletion	35
		Loss of heterozygosity and intragenic mutation	20
BRCA2	13q	Inherited intragenic mutation and loss of heterozygosity	7
MKK4	17p	Homozygous deletion, loss of heterozygosity and intragenic mutation	4
LKB1/STK11	19p	Loss of heterozygosity and intragenic mutation, homozygous deletion	5
ALK5 and *TGF βR2*	9q, 3p	Homozygous deletion	4
DNA mismatch repair			
MSH2, MLH1, others	2p, 3p, others	Unknown	<5

[1]In cases of amplification, it is generally not possible to identify the key oncogene unambiguously due to the involvement of multiple genes.

Table 5.12 Genetic alterations found in pancreatic ductal carcinoma.

Hereditary condition	Mode of inheritance	Gene (chromosomal location)	Lifetime risk of pancreatic cancer
Early onset familial pancreatic adenocarcinoma associated with diabetes (Seattle family)	Autosomal dominant	Unknown	About 30%; 100-fold increased risk of pancreatic cancer; high risk of diabetes and pancreatitis
Hereditary pancreatitis	Autosomal dominant	Cationic trypsinogen (7q35)	30%; 50-fold increased risk of pancreatic cancer
FAMMM: familial atypical multiple mole melanoma	Autosomal dominant	$p16^{INK4A}/CMM2$ (9p21)	10%
Familial breast cancer	Autosomal dominant	BRCA2 (13q12-q13)	5-10%; 6174delT in Ashkenazi Jews, 999del5 in Iceland
Ataxia telangiectasia (heterozygote state)	Autosomal recessive	ATM, ATB, others (11q22-q23)	Unknown; somewhat increased
Peutz-Jeghers syndrome	Autosomal dominant	STK11/LKB1 (19p)	Unknown; somewhat increased
HNPCC: hereditary non-polyposis colorectal cancer	Autosomal dominant	MSH2 (2p), MLH1 (3p), others	Unknown; somewhat increased
Familial pancreatic cancer	Possibly autosomal dominant	Unknown	Unknown; 5-10 fold increased risk if a first-degree relative has pancreatic cancer

Table 5.13 Hereditary conditions predisposing to the development of pancreatic cancer.
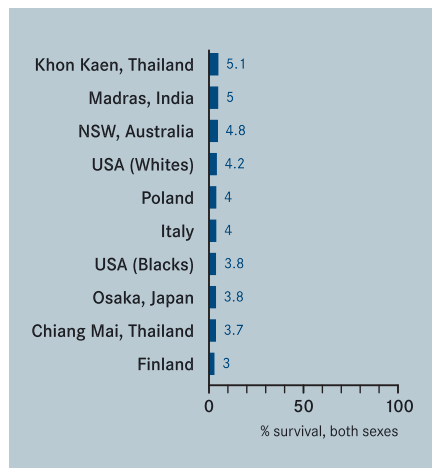

Fig. 5.126 Five-year relative survival rates after diagnosis of pancreatic cancer. Less than 5% of patients survive more than five years.

However, morbidity remains high at 30-40%, and complications are common. In a total pancreatectomy, the entire pancreas, as well as the duodenum, common bile duct, gallbladder, spleen, and nearby lymph nodes are removed. Symptoms of unresectable tumours may also be relieved by surgery.

In Western countries and Japan, different classification systems for staging of pancreatic cancer have evolved, resulting in difficulties in assessing the efficacy of different therapies. Both to overcome the barriers inherent in international classification systems and to achieve a universal prospective data acquisition, a uniform International Documentation System for Exocrine Pancreatic Cancer has been developed by an international group of pancreatologists [13].

Palliative treatment is required for the treatment of jaundice, gastric outlet obstruction and pain. Adjuvant chemotherapy (5-fluorouracil and folinic acid), but not adjuvant radiotherapy, appears to confer a slight survival benefit. Confirmatory trials with newer agents are ongoing. Despite substantial evidence for hormone-dependence of pancreatic cancer, there are no data currently confirming a role for estrogens, androgens, cholecystokinin or their antagonists in clinical treatment of exocrine pancreatic cancer [2].

Survival is poor and the majority of pancreatic cancer patients die within one year of diagnosis, although five-year survival rates can reach >30% for lesions of less than 2 cm, negative lymph nodes and clear surgical margins. In American males, for example, the overall five-year survival rate is 3.7%, and for females, 4.4% (Fig. 5.126).

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WEBSITES

NCI Pancreatic Cancer Homepage:
http://www.cancer.gov/cancer_information/cancer_type/pancreatic/

The Johns Hopkins Medical Institution, Pancreatic Cancer Homepage:
http://www.path.jhu.edu/pancreas/

MELANOMA

SUMMARY

> Approximately 133,000 new cases of malignant melanoma are diagnosed worldwide each year.

> The risk of developing this highly malignant skin tumour varies markedly according to racial background (skin pigmentation) and geography (sunlight-derived ultraviolet irradiation); highest incidence rates occur in white populations in Australia.

> In Nordic countries, a steep increase in melanoma incidence has been attributed to excessive sun exposure during vacations in Southern countries.

> Prognosis for patients with early-stage melanoma is very good, while metastatic melanoma is largely resistant to current therapies.

Fig. 5.127 The global burden of melanoma of the skin in women. Incidence rates are high in North America, Europe, Australia and New Zealand.

Definition

Melanoma is a malignant proliferation of melanocytes, the pigment-forming cells of the skin, which is the site of most (>95%) disease.

Epidemiology

There are about 133,000 new cases of melanoma worldwide each year, of which almost 80% are in North America, Europe, Australia and New Zealand. Incidence is similar in men and in women.

Malignant melanoma of the skin occurs predominantly in white-skinned populations ("Caucasians") living in countries where there is high intensity ultraviolet radiation but this malignancy afflicts to some degree all ethnic groups (Fig. 5.127). Assessed in relation to skin colour, melanoma incidence falls dramatically as skin pigmentation increases and the disease is very rare in dark skinned people.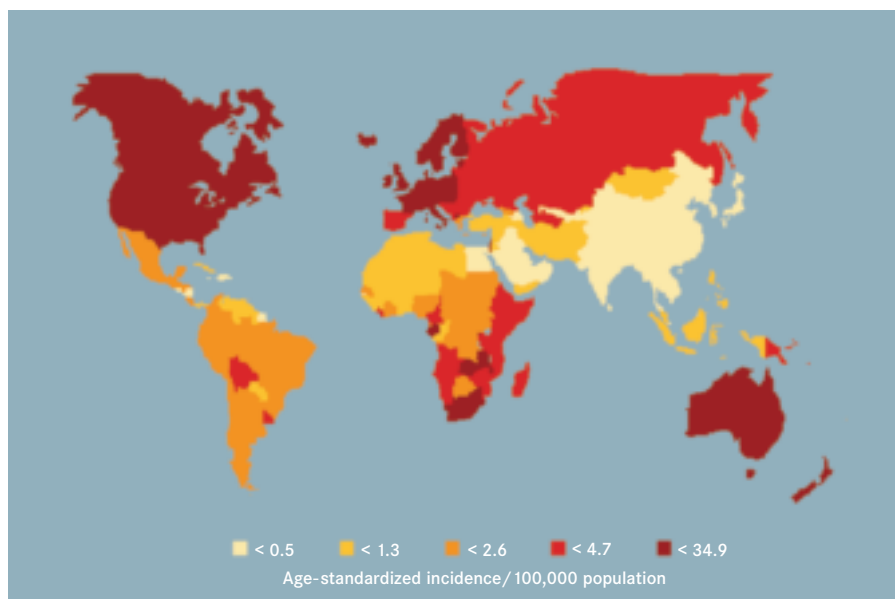 The highest incidence of melanoma occurs in Australia where the population is predominantly white, there is an average of six hours of bright sunlight every day of the year and there is an essentially outdoors lifestyle. The lifetime risk of developing melanoma in Australia is 4-5% in men and 3-4% in women.

Dark-skinned people have a low risk of melanoma. In Africa and South America, the sole of the foot, where the skin is not pigmented, is the most frequent site affected in the context of a low incidence. Asian peoples have a low risk of melanoma despite their paler skins; naevi in Asian people, though common, are predominantly of the acral-lentiginous type which have low malignant potential. Marked increases in incidence and mortality are being observed in both sexes in many countries (e.g. Fig. 5.128), even where rates were formerly low, such as Japan. In the Nordic countries, for example, this averages some 30% every five years. Mortality rates are slightly higher in men than in women, with Australia and New Zealand registering rates of 4.8 and 5.3 for men, and 2.5 and 3.2 for women, respectively [1].

Etiology

It is estimated that 80% of melanoma is caused by ultraviolet damage [2] to sensitive skin, i.e. skin that burns easily, fair or reddish skin, multiple freckles, skin that does not tan and develops naevi in response to early sunlight exposure. Prevention of melanoma is based on limitation of exposure to ultraviolet radiation, particularly in the first 20 years of life (*Reduction of exposure to UV radiation*, p 141).

Ultraviolet radiation is particularly hazardous when it involves sporadic intense exposure and sunburn. Most damage caused by sunlight occurs in childhood and adolescence, making this the most important target group for prevention programmes. Established but rare risk factors include congenital naevi, immunosuppression and excessive use of solaria. While melanoma may occur anywhere on the skin, the majority of melanoma in men is
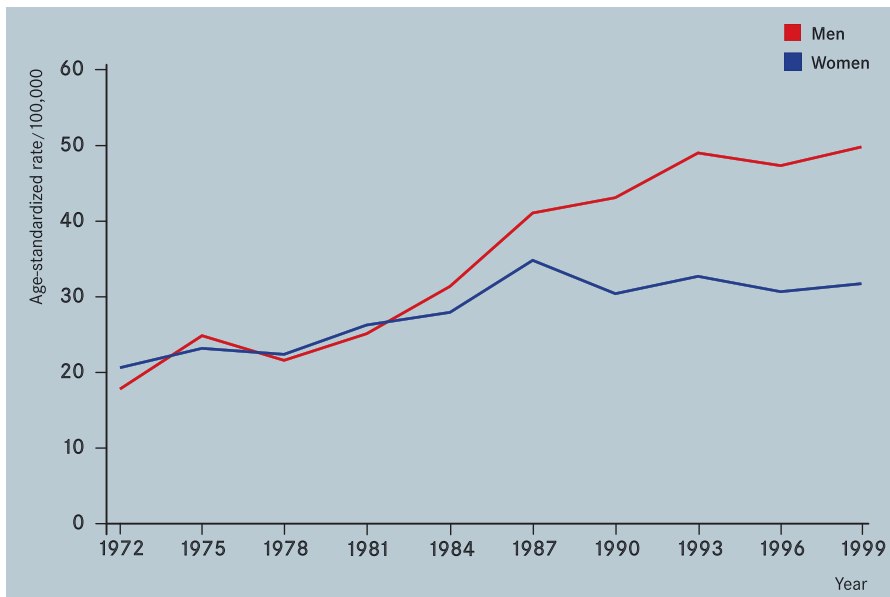
Fig. 5.128 Trends in the incidence of malignant melanoma in New South Wales, Australia.
New South Wales Central Cancer Registry, Australia

on the back, while in women the majority is on the legs. This difference in site incidence is not completely explained by differential exposure to ultraviolet light.

Detection
Melanoma is usually asymptomatic but a person with melanoma sometimes complains of an intermittent itch. Pain, bleeding and ulceration are rare in early melanoma. A melanoma often arises from a pre-existing pigmented lesion of the skin (a mole or "naevus") but these tumours can also develop in unblemished skin. The common predisposing skin lesions are dysplastic naevi, junctional and dermal naevi and blue naevi. However, the risk for melanoma development from mature dermal, junctional and blue naevi is quite small, estimated at approximately 1 in 200,000. Congenital naevi are also known precursors of melanoma but the risk for malignant change is related specifically to the size of the naevus. Naevi greater than 20 mm in diameter and, in particular, the large bathing trunk naevi have a high risk of malignant degeneration. The highest risk naevus is the dysplastic (atypical) naevus. These are naevi that are larger than six mm in diameter, have irregular pigmentation, an ill-defined margin and often exist in multiples. Of particular risk is the dysplastic naevus syndrome (familial atypical mole syndrome) (Fig. 5.130), in which the patient may have more than 100 of these irregular naevi; risk is highest in those patients with dysplastic naevus syndrome who have a near relative diagnosed with melanoma.

The clinical features of melanoma are asymmetry (A), a coastline border (B), multiple colours and quite often some areas of blue/black pigmentation (C), and a diameter greater than six mm (D). As the melanoma progresses, part or all of the lesion will become elevated (E) (Figs. 5.131, 5.132). This ABCDE system has been the basis for clinical diagnosis for melanoma for many years.

Surface microscopy [4] (dermoscopy, epiluminescence microscopy) has developed as an aid to the clinical diagnosis of melanoma. In this technique, the skin surface is rendered translucent by the application of oil and a hand-held instrument providing magnification of at least ten times is used to view the internal details of the tumour. Many additional characteristics, such as pseudopods, radial streaming, blue/grey veil, peripheral black dots and multiple colours are visible and have been used in diagnostic systems now readily accessible to the clinician with an interest in cutaneous diagnosis (Fig. 5.133).

Pathology and genetics
Melanocytes occur primarily in the skin (where more than 95% of cases of melanoma occurs) but are also found in the mucous membranes of the mouth, nose, anus and vagina and, to a lesser extent, the intestine; melanocytes are also present in the conjunctiva, the retina and the meninges. The morphological classification system for melanoma defines four types: superficial spreading melanoma, nodular melanoma, acral-lentiginous melanoma, and lentigo maligna melanoma. However, this classification has been superseded by a system based on the histopathological parameters of the excised lesion. Melanoma is now classified essentially on the vertical diameter of

Fig. 5.129 Intentional sun exposure by holidaymakers on a beach in Nice, France. The majority of cases of melanoma is attributable to sporadic, excessive exposure to ultraviolet radiation which may clinically manifest as sunburn.

Fig. 5.130 Dysplastic naevus syndrome, predisposing to non-familial malignant melanoma. The patient shows atypical cutaneous naevi, usually exceeding 5mm in diameter, with variable pigmentation and ill defined borders.
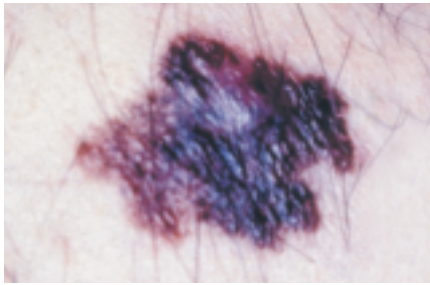
Fig. 5.131 Primary melanoma with a coastline border and multiple colours, including classic blue black pigmentation.
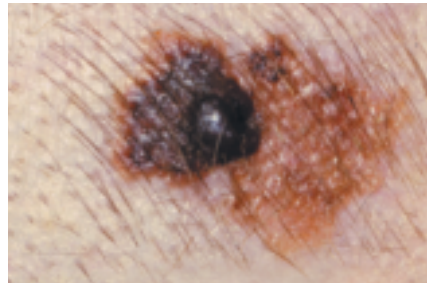

Fig. 5.132 Melanoma with an elevated nodule.

the lesion from the granular cell layer of the epidermis to the deepest detectable melanoma cell (tumour thickness). In recent years, one additional criterion, ulceration, has been shown to be important in prognosis and is included in the AJCC/UICC classification system (Table 5.14).

While it is clear that the genetic make-up of the melanoma-prone population is very important, few melanomas can be ascribed to specific genetic defects in these populations. While 10% of melanoma patients have a first degree relative affected, less than 3% of melanomas in Australia (where the incidence of melanoma is high) can be ascribed to an inherited gene defect [3]. Familial melanoma is even more rare in lower incidence countries.

Loss-of-function mutations in the human melanocortin-1 receptor (MC1-R) have been associated with red hair, fair skin and decreased ability to tan [5], all physical characteristics which affect susceptibility to skin cancer. About 20% of melanoma-prone families possess germline mutations in the *CDKN2*A gene, which encodes p16^{INK4A} [6]. Mutations in the gene encoding CDK4 have been identified but are extremely rare [7].

Genes identified as having a role in sporadic melanoma development include *CDKN2A* and *PTEN*, while chromosomal regions 1p, 6q, 7p and 11q may also be involved [6]. About 20% of melanomas possess mutations in the *p53* gene. Nodular melanomas display amplification of the *MYC* oncogene. Inactivation of p16^{INK4A} is associated with a poorer prognosis. Alterations in the cyclin-dependent kinase PITSLRE have been identified in advanced melanomas [8]. The recent discovery of a role for the *BRAF* gene in melanoma illustrates the impact of large scale international collaboration [9].

Management

Treatment of primary melanoma is essentially surgical and is related specifically to the tumour thickness measurement. The primary tumour is excised with a margin of normal skin, the excision being based on the tumour thickness measurement [10]. As the primary melanoma becomes thicker (deeper), the risk for metastatic spread rises and thus survival outcomes are related specifically to the tumour thickness measurement (Fig. 5.134).

Melanoma metastasizes via the lymphatic system and also via the systemic circulation. Approximately 50% of melanomas metastasize first to the lymph nodes, thus making the management of lymph node metastases an important part of the treatment. Elective lymph node dissection (i.e. prophylactic removal of lymph nodes) is now rarely practised in the management of primary melanoma. The standard management for lymph nodes in patients with primary melanoma is an observation policy and therapeutic node dissection if lymph nodes become involved. However, selective lymphadenectomy [11] is under clinical trial at the present time. This tech-

Classification		Surgical excision margins
Tis	*in situ* melanoma/no invasion of the dermis	5 mm
T1	≤ 1 mm (in thickness)	10 mm
T2	1.1 mm − 2.0 mm	10 mm
T3	2.1 mm − 4.0 mm	Minimum 10 mm, maximum 20 mm
T4	> 4 mm	Minimum 20 mm, maximum 30 mm
	Each T level is classified: A − if ulceration is present B − if no ulceration is present	There is no evidence that a margin greater than 1 cm improves survival but it may decrease local recurrence.

Table 5.14 Classification of melanoma (American Joint Committee on Cancer/International Union Against Cancer) and corresponding recommended excision margins.
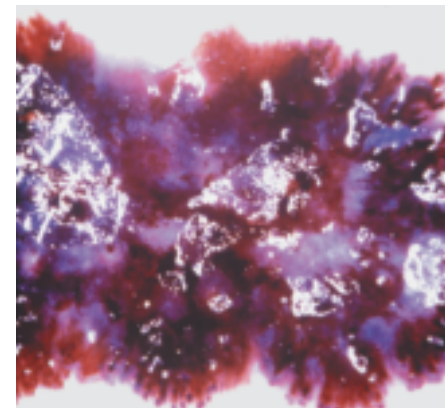

Fig. 5.133 Surface microscopy of a melanoma, showing pseudopods, blue-grey veil and multiple colours.
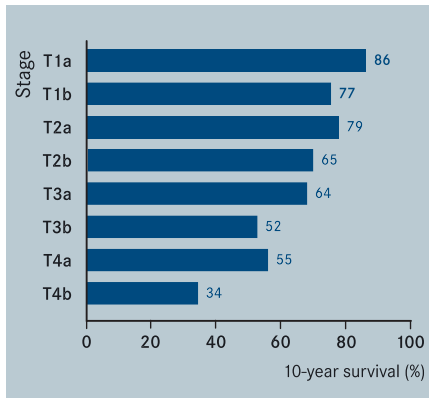
Fig. 5.134 Ten-year relative survival for melanoma, according to stage.

nique enables mapping of the lymphatics in the skin by lymphoscintigraphy: radioactive tracer is injected at the site of the primary and its flow through the skin to the first lymph node that takes up the tracer (the sentinel node) is identified. This lymph node is then removed for histopathological examination; only patients with positive lymph nodes are subjected to full lymph node dissection. However, pending completion of an international trial, the survival benefit of this technique is unknown.

Metastatic melanoma
The greater the number of nodes involved, the higher the risk of systemic metastases and poor prognosis. As the thickness of the melanoma increases and as the number of lymph nodes involved rises, the risk of systemic metastases becomes greater. Melanoma metastasizes widely, with the lungs, liver and brain being the most common sites. Vitiligo (a skin condition characterized by failure to form melanin) is a favourable prognostic sign in metastatic melanoma. At the present time, only a small proportion of people (<5%) live more than two years once systemic metastases become evident [12]. The mainstay for the treatment of systemic metastases is chemotherapy. However, no highly effective single agent or combination has yet been developed and metastatic melanoma is characterized by drug resistance [13]. Spontaneous regression of melanoma, as a result of natural and induced immune rejection, is seen in about 0.4% of cases and this has lead to increasing interest in immunotherapy [14] (*Medical oncology*, p281). At the present time this modality remains experimental, although response rates of 15-20% to cytokines, such as interferon-α and interleukin-2, have been reported, and clinical trials of vaccines containing whole cells, lysates, dendritic cells or melanoma-associated antigens, such as MAGE, TRP and MART, are underway [15].

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WEBSITE

The Melanoma Foundation, Australia:
http://www.medicine.usyd.edu.au/melanoma/

THYROID CANCER

SUMMARY

> Cancer of the thyroid gland is relatively rare, but incidence is increasing in most developed countries. About 120,000 cases occur annually.

> Apart from ionizing radiation, environmental causes have not been well characterized. In Eastern Europe (Belarus, Ukraine, Russia), several hundred children developed thyroid cancer following the Chernobyl accident.

> Prognosis is usually good (around 90% five-year survival for some tumour types), even when lymph node metastases are present.
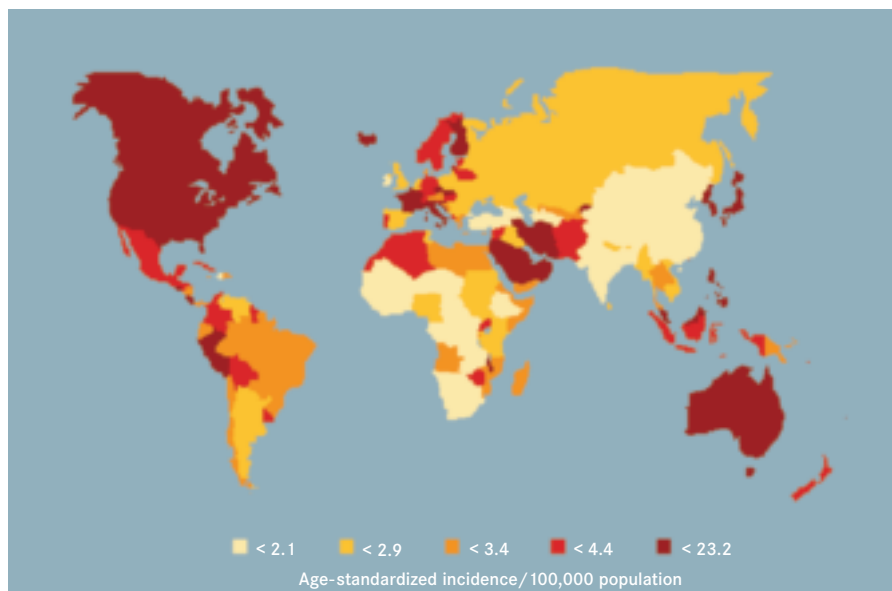
Legend: < 2.1   < 2.9   < 3.4   < 4.4   < 23.2
Age-standardized incidence/100,000 population

Fig. 5.135 Global differences in the incidence of thyroid cancer in women.

Definition

Most thyroid cancers are well-differentiated malignancies, which are predominantly papillary (80-85%), and to a lesser extent, follicular (10-15%) and Hürthle cell carcinomas (3-5%). Anaplastic carcinoma and medullary carcinoma are rare.

Epidemiology

Carcinoma of the thyroid gland is an uncommon cancer although it is the most common malignancy of the endocrine system (Fig. 5.135). Generally, thyroid cancer accounts for approximately 1% of total cancer cases in developed countries. There are about 122,000 new cases per year worldwide.

Incidence of this disease is particularly high in Iceland and Hawaii, where the rate is nearly twice that in North European countries, Canada and USA. In Hawaii, the incidence rate of thyroid cancer in all ethnic groups is higher than in the same ethnic group living in their country of origin and is particularly high among Chinese males and Filipino females. Thyroid tumours are rare in children, less than one case per million per year in most developed countries; the age-specific incidence rates increase rapidly with age (Fig. 5.137). In the past three decades, incidence rates have been increasing in most developed countries, while mortality rates have been slowly decreasing. In the year 2000, the annual mortality rate per 100,000 people was 0.3 for men and 0.6 for women [1]. Thyroid cancer causes some 26,000 deaths every year.

Etiology

An association between thyroid cancer and exposure to ionizing radiation was already suggested in 1950 [2]. Many studies have documented the increased risk of papillary or follicular thyroid carcinoma in individuals exposed to X- and γ-rays [3]. The risk of radiation-induced cancer is considerably greater in those exposed as young children than as adults. Before the Chernobyl accident, epidemiological studies appeared to indicate that radioactive iodines were much less carcinogenic than external X- or γ- irradiation. This is not confirmed by the study of persons exposed as children to fall-out from the Chernobyl accident in the most contaminated territories in Belarus, Ukraine and Russia, where a dramatic increase in thyroid cancer incidence attributable to radioactive iodines has been observed. Iodine deficiency is thought to be involved in the development of thyroid cancer because thyroid cancer incidence rates

Fig. 5.136 The Chernobyl nuclear power plant following the 1986 accident. A marked increase in the incidence of thyroid cancer in children has been observed in areas exposed to radioactive iodine.
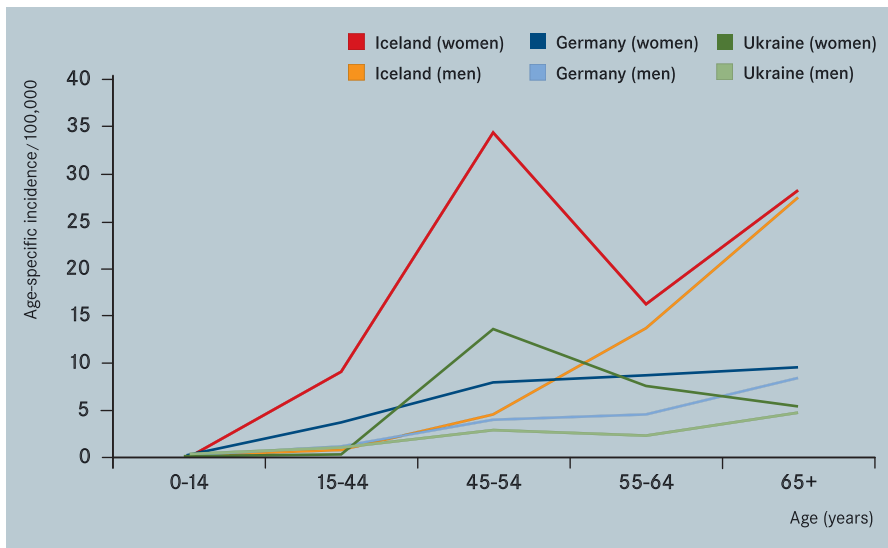
Fig. 5.137 Age-specific incidence of thyroid cancer in men and in women in the Ukraine, Iceland and Germany. Incidence is higher in women and shows a marked peak.

are high in mountainous areas, such as the Alps, Andes, and Himalayas, where severe iodine deficiency was or still is common [4]. However, several high-risk populations live on islands (such as Hawaii and Iceland), where iodine intake is generally high. The relationship between iodine intake and risk of thyroid cancer appears to be complex, since both deficiency and excess may inhibit the synthesis of thyroid hormones and cause goitre [5]. The two main types of thyroid carcinoma (papillary and follicular) may be linked to iodine-rich and iodine-deficient diets, respectively [6]. Other dietary factors, including cruciferous and goitrogenic vegetables [7], may play a role in thyroid carcinogenesis.

Thyroid cancer occurs approximately three times more frequently in women than in men, reaching a maximum at about age 45. Hormonal factors may play a role in etiology. Results from epidemiological studies, however, have been inconsistent: some have found an association between parity and risk of thyroid cancer while others did not. The most current data suggest that menstrual and reproductive factors are weakly related to thyroid cancer risk [8]. Apart from irradiation in childhood, goitre and benign nodules

are the strongest risk factors with a relative risk of approximately 3 and 30, respectively [9]. The role of hypothyroidism and hyperthyroidism is less clear.

Detection

Thyroid cancer commonly causes no obvious symptoms in its early stages. The vast majority of cancers become clinically evident as thyroid nodules. However, only a minority of all thyroid nodules is malignant. Many nodules are found in asymptomatic patients on physical examination of the neck. Some cases have a history of rapid increase in size and/or pain in the region of the nodule. Hoarseness, dyspnoea and dysphagia reflect local invasion of the recurrent laryngeal nerve, trachea and oesophagus, respectively. A small subset of patients presents with palpable cervical lymphadenopathy without an identifiable thyroid primary. High-resolution ultrasonography is useful for size assessment of nodules and for detection of unpalpable nodules. Differences in echogenicity, vascularity or tests of thyroid function cannot distinguish benign from malignant nodules. The single most important diagnostic procedure is the fine needle aspiration biopsy, performed under ultrasound guidance.

Pathology and genetics

Thyroid follicular cells give rise to both well-differentiated cancers and also to poorly differentiated and undifferentiated (anaplastic) cancers. Well differentiated cancers are further classified into papillary and follicular carcinomas and other rare types. Stromal and immune cells of the thyroid are responsible for sarcoma and lymphoma, respectively. Approximately 90% of malignant thyroid nodules are well-differentiated cancers.

Papillary and follicular cancers have the lowest degree of clinical malignancy. Papillary carcinoma has a propensity to invade lymphatic spaces and leads to microscopic multifocal lesions in the gland and a high incidence of regional lymph node metastases. Follicular carcinoma is unifocal and thickly encapsulated. It has a propensity to invade veins and not lymphatics.

Thyroid parafollicular cells (C cells) give rise to medullary carcinomas which usually produce calcitonin.

Insular (poorly differentiated) carcinomas are considered to be of intermediate differentiation and consequently to exhibit

Fig. 5.138 Clinical examination of the thyroid gland of a child at risk following radioactive exposure as a result of the Chernobyl accident.
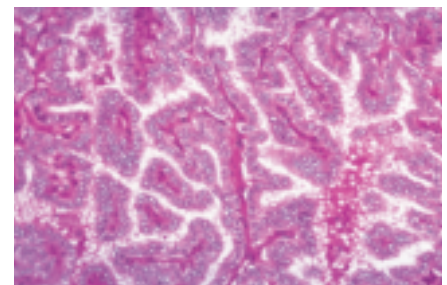

Fig. 5.139 Histopathological features of a papillary thyroid carcinoma.
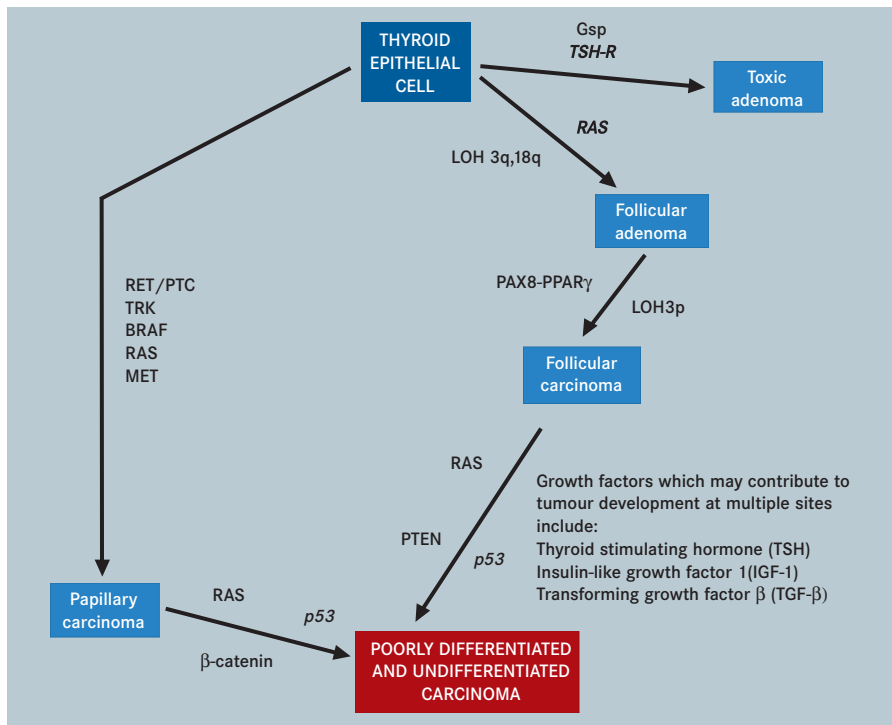
Fig. 5.140 Proposed genetic model of thyroid tumour formation. Genes in bold type have a well-established role.

an intermediate degree of clinical malignancy. Insular carcinoma invades both lymphatics and veins, and nodal and distant metastases are common.

Approximately 33% of tumours displaying oncocytic (Hürthle cell) features show histological evidence of malignancy (e.g. nuclear features typical of papillary carcinoma) or invasive growth. The remainder behave as adenomas and may be treated conservatively.

There is evidence of familial risk in a small percentage of papillary and follicular thyroid carcinomas. The associations of Gardner syndrome (familial adenomatous polyposis) and Cowden disease (familial goitre and skin hamartomas) with differentiated thyroid carcinoma provide well-defined examples. About 25 to 35% of all medullary thyroid carcinomas are identified as a component of one of the clinical syndromes. These syndromes include: multiple endocrine neoplasia type 2A (MEN2A) which is associated with medullary thyroid carcinoma, pheochro-

mocytoma and hyperparathyroidism; multiple endocrine neoplasia type 2B (MEN2B) which is associated with medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, and marfanoid-like features; and familial medullary thyroid carcinoma.

The genes implicated in the pathogenesis of thyroid carcinoma generally form a subset of important cell growth and differentiation regulatory factors that can be separated into membrane and nuclear factors. Two different mechanisms are involved in the genesis of papillary thyroid and medullary thyroid carcinomas. As a result of intrachromosomal rearrangements, the RET proto-oncogene becomes attached to the promoter of one of three genes expressed constitutively in the follicular cell, which results in the so-called "papillary thyroid carcinoma oncogene" (RET/PTC 1, 2, and 3). Germline point mutations of the RET proto-oncogene, which is normally expressed in the thyroid parafollicular

cell, are found in more than 95% of individuals with hereditary medullary thyroid carcinoma (codons 609, 611, 618, 620, or 634). Mutation of codon 634 is the most commonly observed and is found in about 80% of all patients with hereditary medullary thyroid carcinoma. A germline point mutation in the tyrosine kinase portion of the RET receptor (codon 918) has been identified in 95% of individuals with MEN2B [10].

Management

Patients with malignant lesions diagnosed on the basis of fine needle aspiration, as well as patients with a suspicious aspiration, combined with other risk factors (such as prior radiation exposure or local symptoms) should have surgical resection. It has been recommended that total thyroidectomy should be performed at around the age of six years in children who are MEN2A gene carriers and shortly after birth in children with the MEN2B mutation [11]. Benign nodules can be monitored by ultrasound examination. Acceptable surgical procedures include lobectomy, subtotal thyroidectomy, near-total thyroidectomy and total thyroidectomy. Modified radical neck dissection is indicated in case of lymph node metastases. All patients who have undergone a total or near-total thyroidectomy for a papillary or follicular car-
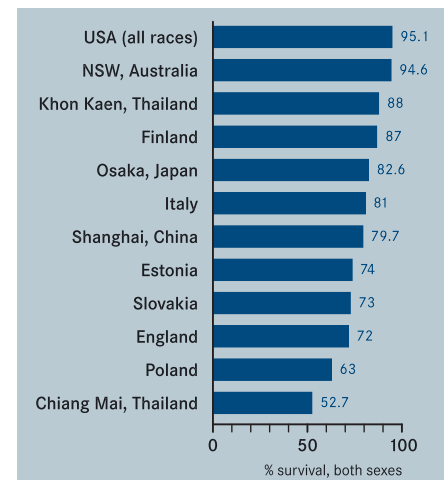

Fig. 5.141 Five-year relative survival after diagnosis of thyroid cancer.

cinoma of greater than 1.5 cm should be considered candidates for radioiodine ablation [12].

In contrast to other solid neoplasms, the presence of regional lymph node metastases with a well-differentiated thyroid cancer has no strong correlation with overall survival. Independent predictors of prognosis include patient's age, gender, tumour size, histological grade and type, local invasion, multicentricity and the presence of systemic metastatic disease. Five-year relative survival rates for this type of malignancy vary greatly according to histological type, ranging from 98% for papillary carcinoma and 92% for follicular carcinoma, to 11% for anaplastic carcinoma [13]. Overall five-year survival rates vary significantly geographically (Fig. 5.141).

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WEBSITES

The British Thyroid Association:
http://www.british-thyroid-association.org/

The European Thyroid Association:
http://www.eurothyroid.com/

KIDNEY CANCER

SUMMARY

> Cancer of the kidney is the 15th most common cancer in the world and most prevalent in developed countries. Close to 190,000 cases are diagnosed each year worldwide and men are generally affected more frequently than women.

> Tobacco smoking is an established cause. Excess body weight (obesity) has also been identified as a risk factor, particularly in women.

> Patients with late stage diagnosis face a poor prognosis. Recent advances in imaging allow the early detection of asymptomatic tumours. The five-year survival rate is approximately 50%.
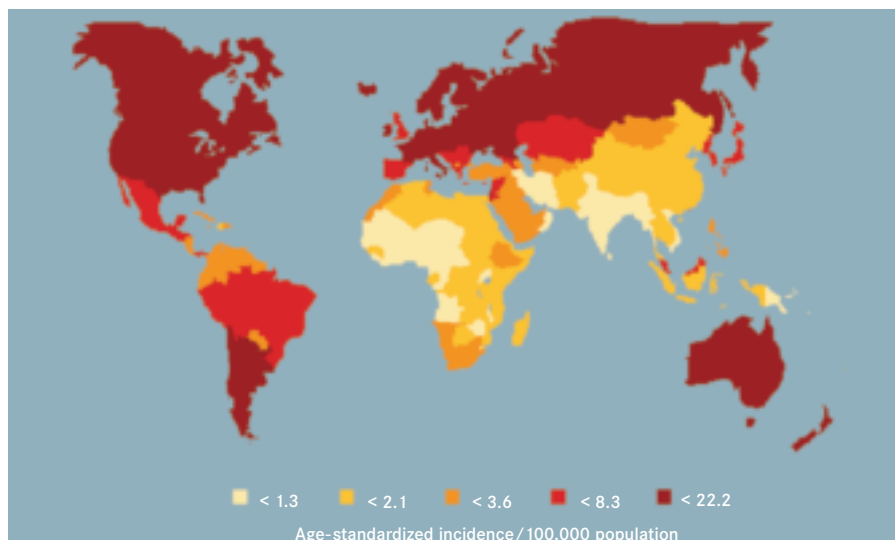
Age-standardized incidence/100,000 population: < 1.3, < 2.1, < 3.6, < 8.3, < 22.2

Fig. 5.142 Global burden of kidney cancer in men, showing a generally higher incidence in more developed countries.

Definition

In adults, 85-90% of cases of kidney cancer are renal cell carcinomas, a very heterogeneous group of tumours (mainly adenocarcinomas) which arise from cells of the proximal convoluted renal tubule. Transitional cell carcinoma is a less common tumour type that arises from the transitional cell epithelium in the renal pelvis, ureter and urethra. Wilms tumour (nephroblastoma) is an embryonal malignancy that afflicts 1 in 10,000 children.

Epidemiology

The incidence of kidney cancer is considerably higher in developed countries than in less developed countries (Fig. 5.142) and appears to be increasing over the past decade [1,2]. More than 189,000 new cases are diagnosed worldwide each year. In Western Europe, for example, kidney cancer is the sixth most frequently occurring cancer, incidence being particularly high in the Bas-Rhin region of France [3]. Incidence is also exceptionally high in the Czech Republic and among Scandinavian populations. Kidney cancer is relatively less common among Asian and African peoples, although renal cell carcinoma appears to be increasing in black American men [4]. Men are affected by kidney cancer more than women, the sex ratio being 1.6-2.0:1 [5]. Most cases occur between ages 50-70, but kidney cancer may be diagnosed over a broad age range including young adults [1]. Wilms tumour is responsible for 5-15% of childhood cancers, affecting females slightly more than males. This tumour occurs with highest frequency in the black population of USA and Africa, and with lowest in Eastern Asia [1]. Kidney cancer causes the deaths of more than 91,000 people each year.

Etiology

Kidney cancer has consistently been found to be more common in cigarette smokers than in non-smokers. The association was first established as causative for transitional cell carcinoma of the bladder and has now been extended to renal cell carcinomas, the risk increasing two-fold for heavy smokers [6]. An increased risk of renal cell carcinoma has been linked to obesity, particularly in women, as has diuretic therapy, again especially in women [7]. Leather tanners, shoe workers and dry cleaning employees have an increased risk as reported in some studies, as do workers exposed to asbestos and trichloroethylene. The influence of beverages, in particular coffee and alcohol, has not been clearly determined despite many studies. Phenacetin is carcinogenic: patients with kidney damage secondary to phenacetin-containing analgesic abuse have an increased risk of transitional cell carcinoma (*Medicinal drugs*, p48). Patients with multicystic kidney disease consequent on long-term dialysis, adult polycystic kidney disease and tuberous sclerosis also have an increased propensity to develop renal cell carcinoma and von Hippel-Lindau disease, an autosomal dominant condition, is a predisposing factor.

Fig. 5.144 A patient receiving kidney haemodialysis: long-term dialysis predisposes to acquired cystic disease of the kidney which may increase the risk of subsequent cancer.
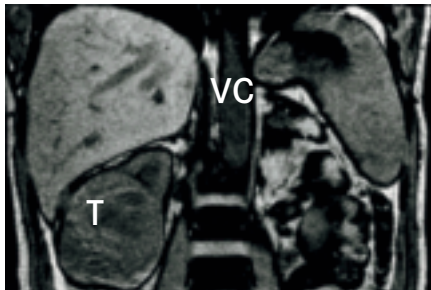

Fig. 5.145 Magnetic resonance image of a renal cell carcinoma (T), with a tumour thrombus in the inferior vena cava (VC).

Detection

Kidney cancer commonly causes no obvious symptoms in its early stages. Subsequently, symptoms include haematuria, loin pain and a palpable kidney mass [8] and these usually indicate patients with advanced disease. As a consequence of increasing use of renal imaging techniques, increasing numbers of asymptomatic, incidental tumours are being detected [5]. Diagnosis of renal cell carcinoma may be preceded by paraneoplastic syndromes, the systemic and humoral manifestations of the disease, which result from the overproduction of normal kidney proteins or hormones (e.g. renin, erythropoetin, prostaglandins) or inappropriate expression of non-kidney factors (e.g. parathyroid hormone). Symptoms may include hypertension, fever, anaemia, erythrocytosis (elevated number of red blood cells), abnormal liver function and hypercalcaemia (abnormally high calcium levels) [2, 8].

The presence of a tumour may be initially defined by intravenous urogram. Computed tomography (CT) is the imaging procedure of choice for diagnosis and staging [1]; scanning of the abdomen and pelvis confirms tumour extent, lymph node status and contralateral kidney functionality. Selective renal arteriography via percutaneous femoral artery catheterization may be used for diagnosis and staging [1]. Less invasive than arteriography is magnetic resonance imaging (MRI), which can also be used to assess thrombus of renal vein or vena cava involvement (Fig. 5.145). Chest radiographs (commonly with CT) and technetium-99m radiopharmaceutical bone scans are employed to determine whether lung or skeletal metastases are present.

Pathology and genetics

Renal cell carcinoma (Figs. 5.146, 5.147) is commonly represented by adenomas, although there is some controversy over the difference between renal cortical adenoma and renal cell adenocarcinoma [1]. In terms of renal cell carcinoma histology, grade I cells have a lipid-rich cytoplasm and a small peripheral nucleus. As grade advances from I to IV, the nuclear pleomorphism increases and the lipid-rich cytoplasm reduces. The tumour is initially capsulated (in 50-60% of diagnosed cases), tends to spread to lymph nodes (10% of cases diagnosed) or may metastasize to the lungs, bone, brain and liver (20-30% of cases). There is a tendency for the tumour to spread within the renal vein and into the inferior vena cava, extending in extreme cases into the right atrium [8]. Transitional cell carcinoma accounts for 5-8% of kidney tumours [8] and is derived from the renal pelvis transitional cell epithelium, which is identical to that of the bladder and ureter; 50% of patients with renal transitional cell carcinoma also develop the same tumour type of the bladder.

Cytogenetics and molecular biology have allowed significant advances to be made in the differentiation and staging of kidney cancer tumours, which may be histologically complex and heterogeneous [9].

Cytogenetics have shown, for example, that the two main types of renal cell carcinomas, clear cell (non-papillary) carcinoma and papillary carcinoma, are genetically distinct (Table 5.15), although there can often be difficulties in distinguishing them histologically. Corresponding changes in transitional cell carcinoma have been less well-defined. The papillary form has a better prognosis than the non-papillary [9]. Mitochondrial DNA changes have been observed in early-stage oncocytic and chromophobe tumours [10], but are not yet used clinically.

Von Hippel-Lindau disease is characterized by the development of multiple tumours, including bilateral renal cell carcinoma, pheochromocytomas, hemangioblastomas of the central nervous system, retinal angiomas and pancreatic cysts [1,11]. Von Hippel-Lindau patients have a >70% lifetime risk for renal cell carcinoma and it is the cause of death in 15-50% of cases. Such patients thus require regular screening; currently some 30-50% of patients with von Hippel-Lindau disease who are identified with renal cell carcinoma as a result of symptoms have metastases on presentation, and hence respond poorly to treatment. Most families with von Hippel-Lindau disease (80%) have mutations in the *VHL* gene, a probable tumour suppressor gene. Sporadic forms of renal cell carcinoma, as well as familial forms, are asso-
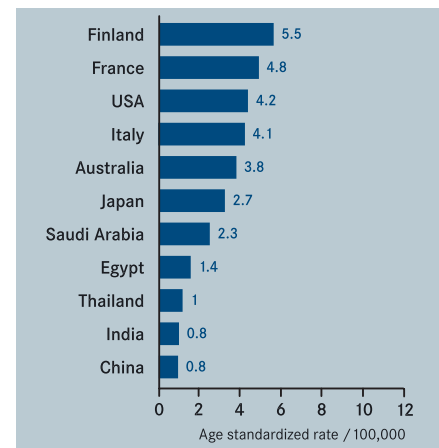

Country	Age standardized rate / 100,000
Finland	5.5
France	4.8
USA	4.2
Italy	4.1
Australia	3.8
Japan	2.7
Saudi Arabia	2.3
Egypt	1.4
Thailand	1
India	0.8
China	0.8

Fig. 5.143 Mortality from kidney cancer in various countries.

Stage	Clear cell carcinoma	Papillary carcinoma
Adenoma	Loss of 3p Partial trisomy of 5q Loss of Y chromosome	Loss of Y chromosome Trisomy of 7, 17 Gain of 3p Gain of 7, 12, 16, 17, 20
Carcinoma	p53 mutations Loss of 8, 9, 13, 14, 6q, 10q, 18q, 11, 17/17p Gain of 12, 20 Loss of VHL function	Loss of 6q, 9, 11, 14q, 17/17p, 21 Gain of 8, 20 Loss of MET function
Metastatic tumours		Excess of minichromosomes, comprising 7q31 containing the MET oncogene

Table 5.15 Genetic alterations in renal cell carcinoma.

Fig. 5.146 Surgical specimen of a bisected kidney showing a large renal cell carcinoma. Much of the kidney has been replaced by tumour tissue.

ciated with structural alterations of the short arm of chromosome 3 and with VHL gene mutations [1,11].

Wilms tumour of the kidney occurs in both sporadic and familial forms. It has a specific syndrome associated with abnormalities including aniridia (absence of the iris), hemihypertrophy (overgrowth of one half of the body or a body part), and cryptorchidism (failure of the testes to descend into the scrotum). A number of loci involved in the development of Wilms tumour have been characterized, key amongst these being WT1, a tumour suppressor gene located on chromosome 11p [12].
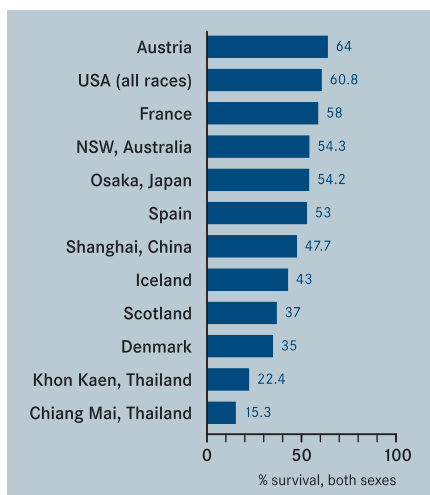

Fig. 5.148 Five-year relative survival after diagnosis of kidney cancer.

Management

Radical nephrectomy (removal of the kidney, perinephric fat, adjacent lymph nodes and often the adrenal gland) is currently the main therapy for renal cell carcinoma. This procedure has been shown to produce better survival rates than simple nephrectomy (kidney removal only), since involvement of regional lymphatics and periaortic lymph nodes has been noted in almost 25% of patients [1]. Treatment for transitional cell carcinoma is radical nephroureterectomy, although more conservative therapy may be appropriate for smaller low-grade tumours. In patients possessing a single kidney, or in the case of bilateral simultaneous tumour, either partial nephrectomy or radical nephrectomy with dialysis and possible later transplantation is indicated [1]. However, immunosuppression associated with transplantation raises the risk of potential tumour recurrence (*Immunosuppression*, p68).

Accurate staging depends on histological evaluation of the resected tumour. Up to 30% of patients present with metastases at diagnosis or relapse following surgery. Metastatic kidney cancer is extremely resistant to systemic therapy [13]. A potential reason for this is the high level of expression of the multi-drug resistance gene MDR1 which encodes P-glycoprotein (Box: *Resistance to cancer chemotherapy*, p285) in both normal proximal tubules and in tumour
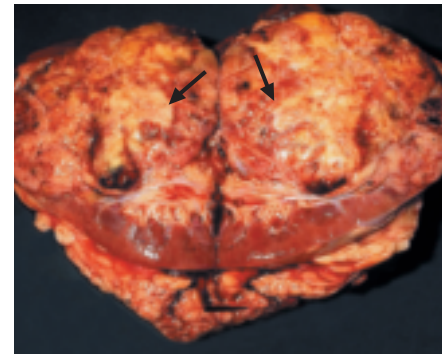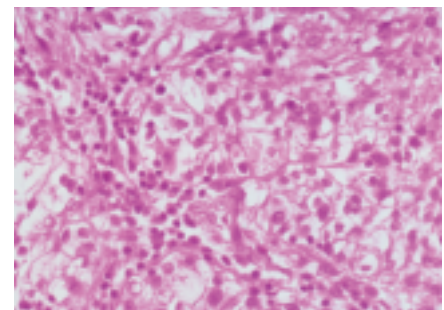

Fig. 5.147 Clear cell carcinoma of the kidney showing a monomorphic proliferation of distinctive tumour cells, with an abundant clear, lipid-containing cytoplasm, arranged in a trabecular pattern.

tissue [14]. Most chemotherapeutic and hormonal agents appear to show little efficacy, although there is some controversy over the efficacy of vinblastine and 5-fluorouracil as single agents or in combination therapy [13,8]. In contrast, in the treatment of transitional cell carcinoma, cisplatin combination therapy seems to be effective.

For the systemic treatment of metastatic kidney cancer, interferon-α and interleukin-2 have been shown to elicit a modest response rate of 10-15% [8], allowing complete response in some patients and an increased survival benefit in others. Although overall survival rates are poor (Fig. 5.148), the five-year survival for patients with early stage tumours is greater than 80% [8]. The indication of renal vein/inferior vena

cava involvement reduces five-year survival rates to 25-50%, whilst regional lymph node involvement or extracapsular extension also indicates a much reduced rate of 15-50%. The presence of distant metastases or stage IV cancer carries a very poor prognosis (5% five-year survival rate) [1].

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WEBSITES

NCI Kidney Cancer Homepage:
http://www.cancer.gov/cancer_information/cancer_type/kidney/

The Kidney Cancer Association (USA):
http://www.nkca.org/

TUMOURS OF THE NERVOUS SYSTEM

SUMMARY

> Tumours of the nervous system account for less than 2% of all malignancies (about 175,000 cases per year worldwide); the incidence does not vary markedly between regions or populations.

> Etiology is largely unknown; the only unequivocal cause is therapeutic irradiation, but occurrence in these circumstances is very rare.

> The nervous system is frequently involved in inherited tumour syndromes, including neurofibromatosis (*NF1/NF2* germline mutations), von Hippel-Lindau disease (*VHL*), tuberous sclerosis (*TSC1/TSC2*) and Li-Fraumeni syndrome (*p53*).

> Glioblastomas are the most common brain tumours and mainly affect adults. These tumours are surgically incurable and largely resistant to radiation and chemotherapy; only 3% of patients survive more than 3 years.

> Embryonal tumours, including cerebellar medulloblastomas, retinoblastomas and peripheral neuroblastoma, predominantly afflict children, ranking second after leukaemia as the most common types of paediatric cancer.

Fig 5.149 Incidence of cancers of the brain and nervous system in men, in Europe.

Definition

The majority of tumours of the central nervous system (CNS) are derived from glial cells (gliomas), the most malignant and frequent being glioblastoma. Malignant embryonal tumours typically manifest in children and occur in the central nervous system (medulloblastomas) and the sympathetic nervous system and adrenal gland (neuroblastomas). Tumours originating from the brain coverings (meningiomas) are usually benign.
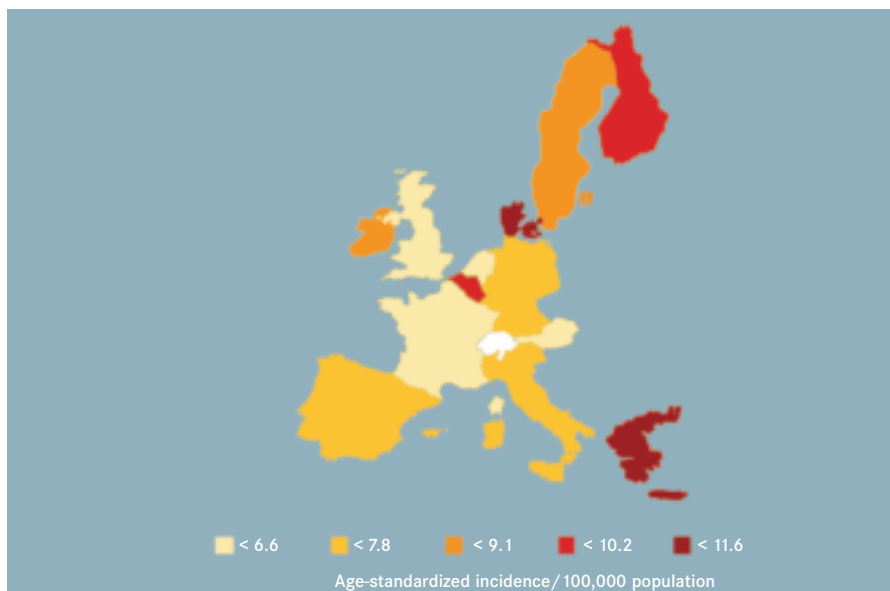
Epidemiology

The age distribution of brain tumours is bimodal, with a peak incidence in children and a second larger peak in adults aged 45-70 [1]. In most developed countries, brain tumours are the 12th most frequent cause of cancer-related mortality in men [2]. Geographical variation in incidence is less than for most other human neoplasms [2] (Fig. 5.149). However, incidence tends to be higher in more developed countries. In most North American and European countries, incidence rates for malignant tumours of the nervous system are 6-8 new cases per 100,000 population per year. Highest rates are observed in Sweden, Greece, Iceland and Croatia. In multiracial communities, both adults and children of African or Asian descent tend to be less frequently affected than whites. It has been reported that white Americans have a 3.5 times greater risk of glioblastoma and germ cell tumours than African Americans [1]. However, the lower incidence recorded for Singapore and Japan may be due to inadequate registration.

Generally, incidence rates are higher for men; in particular, malignant brain tumours occur more frequently in males while the benign meningiomas occur predominantly in females. During the past decade, the incidence of glioblastomas in the elderly has increased by 1-2% per year but to some extent this may be due to the introduction of high-resolution neuroimaging. The brain is also a frequent site of metastases, with carcinomas of the breast and lung as most frequent primary tumours.

Etiology

With the exception of brain tumours associated with inherited cancer syndromes and the very rare cases caused by therapeutic irradiation, no causative environmental or lifestyle factors have been unequivocally identified. Radiation-induced meningiomas may follow low-dose irradiation for tinea capitis (a fungal infection of the scalp) and high-dose irradiation for primary brain tumours [3]. Children who received prophylactic CNS irradiation for acute lymphoblastic leukaemia seem to have an increased risk of developing malignant gliomas.

Tumour (WHO Grade)	Typical location	Age at clinical manifestation (% of cases)			Five-year survival (% of patients)	Genetic alterations
		0-20 yrs	20-45 yrs	>45 yrs		
Pilocytic astrocytoma (Grade I)	Cerebellum, optic nerve	74	20	6	>85	*NF1* (neurofibromatosis cases)
Low grade diffuse astrocytoma (Grade II)	Cerebral hemispheres	10	61	29	>50	*p53* mutation
Glioblastoma (Grade IV)	Cerebral hemispheres	3	25	72	<3	*EGFR* amplification, *PTEN* mutation, p16 deletion, LOH chromosome 10
Oliogodendroglioma (Grade II/III)	Cerebral hemispheres	8	46	46	>50	LOH 1p, 19q
Ependymoma (Grade II)	Ventricles, spinal cord	37	38	25	<30	*NF1* (spinal tumours)
Medulloblastoma (Grade IV)	Cerebellum	74	23	3	>50	Isochromosome 17, mutations of *p53*, *PTCH*, ß-catenin
Neuroblastoma (Grade IV)	Abdomen	>95			>90 (<1 yr old) 20-50 (>1 yr)	LOH 1p, 11q, *MYCN* amplification, trisomy 17q

Table 5.16 Summary of epidemiological data on intracranial tumours.

Some studies have suggested an increased incidence of CNS neoplasms associated with certain occupations, including farming, fire-fighting, metalworking and the rubber and petrochemical industries, and with those who work as anatomists, pathologists and embalmers, but most of these reports have not been confirmed and causative agents have not been identified. Suggestions that radiofrequency radiation generated by mobile phones and microwave telecommunications may play a role in the etiology of

Fig 5.150 A large glioblastoma multiforme in the left frontal lobe, extending into the corpus callosum and the contralateral white matter.

malignant gliomas remain to be substantiated. Similarly, the role of diet in brain tumour etiology, and specifically involvement of *N*-nitroso compounds (which are potent neuro-carcinogens in rodents) formed in nitrite-preserved food, is unclear.

The nervous system is frequently affected in inherited tumour syndromes, often in association with extraneural tumours and skin lesions (Table 5.17).

Detection

Signs and symptoms largely depend on the location of the neoplasm and include paresis (slight/incomplete paralysis), speech disturbances and personality changes. Patients with oligodendroglioma often have a long history of epileptic seizures. Eventually, malignant brain tumours cause life-threatening intracranial pressure that may result in visual disturbance and ultimately lead to unconsciousness and respiratory arrest. Since the brain does not contain pain receptors, headache is only present if the tumour infiltrates the meninges. The presence of symptoms usually leads to a detailed neurological examination, using techniques such

as computed tomography (CT) and magnetic resonance imaging (MRI).

Pathology and genetics

The WHO classification of tumours of the nervous system contains more than 50 clinico-pathological entities with a great variation in biological behaviour, response to therapy and clinical outcome [4]. The most frequent ones are listed in Table 5.16. Of all intracranial tumours, approximately 60% are of neuroepithelial origin (gliomas), 28% are derived from the brain coverings (meningiomas) and 7.5% are located in cranial and spinal nerves. Lymphomas and germ cell tumours account for 4% and 1% respectively.

Astrocytic tumours

Tumours of astrocytic origin constitute the largest proportion of gliomas. They vary greatly in morphology, genetic profile and clinical behaviour.

Pilocytic astrocytoma (WHO Grade I) is the most frequent CNS neoplasm in children, and is predominantly located in the cerebellum and midline structures, includ-
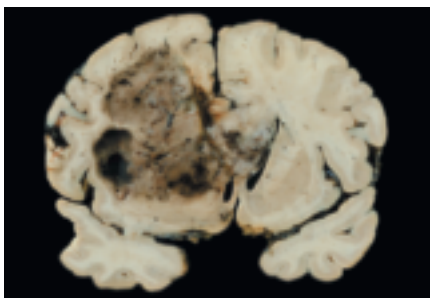
ing the optic tract, brain stem and spinal cord. It infiltrates adjacent brain structures but grows slowly and usually has a favourable prognosis with five-year survival rates of more than 85% (WHO Grade I). Some pilocytic astrocytomas occur in the setting of neurofibromatosis type 1 (NF1), particularly those of the optic nerve (optic glioma). Other astrocytomas usually develop in the cerebral hemispheres of adults and diffusely infiltrate adjacent brain structures.

Low grade diffuse astrocytomas (WHO grade II) occur in young adults and grow slowly. However, they diffusely infiltrate the brain and cannot, therefore, be completely surgically resected. Morphologically, tumour cells resemble differentiated astrocytes. Mutations in *p53* are found in two-thirds of cases and are considered an early event. The five-year survival rate is more than 60%.

Anaplastic astrocytomas (WHO grade III) often develop from low-grade astrocytomas, grow relatively fast and typically progress to glioblastoma within two to three years, accompanied by genetic alterations, including loss of heterozygosity (LOH) on chromosome 19.

Glioblastomas (WHO grade IV)

This is the most frequent and most malignant nervous system tumour. Secondary glioblastomas develop by malignant progression from low-grade and anaplastic astrocytoma and are characterized by *p53* mutations and LOH on chromosome 10q. Primary glioblastomas are more frequent (>80% of cases) and develop rapidly in the elderly (mean age, 55 years), with a short clinical history of less than three months. Their genetic profile includes amplification and overexpression of the *EGF* receptor gene, *PTEN* mutations, p16^{INK4A} deletions and loss of chromosome 10. Both glioblastoma types diffusely infiltrate the brain, including the opposite hemisphere and show high cellularity and large areas of necrosis despite excessive vascular proliferation.

Oligodendrogliomas

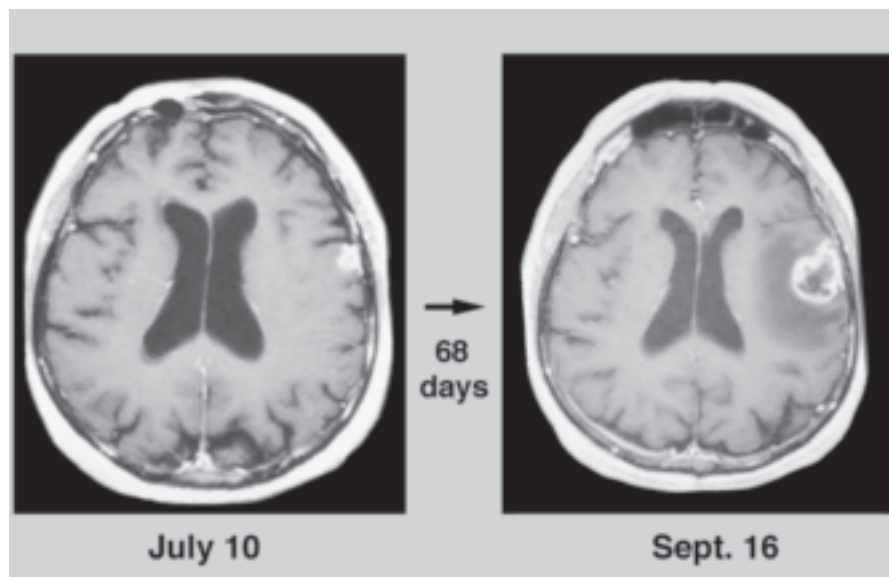These neoplasms develop from myelin-producing oligodendroglial cells or their

Fig. 5.151 An MRI scan of a primary glioblastoma in a 79 year-old patient. A small cortical lesion rapidly developed into a full-blown glioblastoma with perifocal oedema and central necrosis.

precursors and are typically found in the cerebral hemispheres of adults, often including the basal ganglia. Histologically, they are isomorphic, with a typical honeycomb pattern and delicate tumour vessels ("chicken wire" pattern). Anaplastic oligodendrogliomas (WHO Grade III) show features of anaplasia and high mitotic activity and carry a less favourable prog-nosis. Genetic hallmarks of oligodendrogliomas are LOH on chromosomes 1p and 19q. Oligodendrogliomas that carry these genetic alterations show a remarkable sensitivity to chemotherapy.

Ependymomas

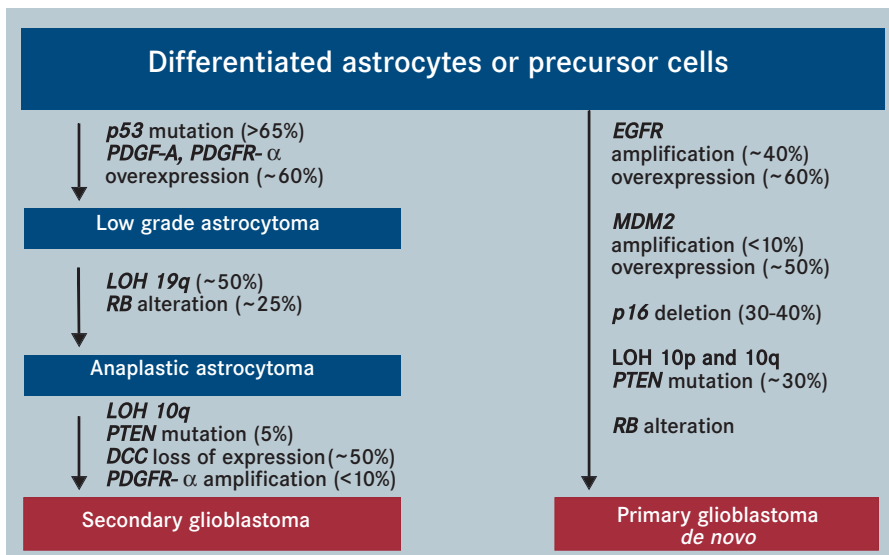These gliomas develop from the ependymal lining of the cerebral ventricles and

Fig 5.152 Genetic pathways in the evolution of primary and secondary glioblastoma.

Syndrome	Gene	Chromo-some	Nervous system	Skin	Other tissues
Neurofibromatosis 1	*NF1*	17q11	Neurofibromas, MPNST, optic nerve gliomas, astrocytomas	Café-au-lait spots, axillary freckling	Iris hamartomas, osseous lesions, phaeochromocytoma, leukaemia
Neurofibromatosis 2	*NF2*	22q12	Bilateral vestibular schwannomas, peripheral schwannomas, meningiomas, meningioangio-matosis, spinal ependymomas, astrocytomas, micro-hamartomas, cerebral calcifications	-	Posterior lens opacities, retinal hamartoma
von Hippel-Lindau	*VHL*	3p25	Haemangioblastomas	-	Retinal haemangioblastomas renal cell carcinoma,
Tuberous sclerosis	*TSC1* *TSC2*	9q34 16p13	Subependymal giant cell astrocytoma, cortical tubers	Cutaneous angiofibroma ("adenoma sebaceum") peau de chagrin, subungual fibromas	Cardiac rhabdomyomas, adenomatous polyps of the duodenum and the small intestine, cysts of the lung and kidney, lymphangioleiomyomatosis, renal, angiomyolipoma
Li-Fraumeni	*p53*	17p13	Astrocytomas, glioblastomas, medulloblastomas	-	Breast carcinoma, bone and soft tissue sarcomas, adrenocortical carcinoma, leukaemia
Cowden	*PTEN (MMAC1)*	10q23	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos), megalencephaly	Multiple trichilemmomas, fibromas	Hamartomatous polyps of the colon, thyroid neoplasms, breast carcinoma
Turcot	*APC*	5q21	Medulloblastoma	-	Colorectal cancer
	hMLH1 *hPSM2*	3p21 7p22	Glioblastoma	Café-au-lait spots	Colorectal cancer
Naevoid basal cell carcinoma syndrome (Gorlin)	*PTCH*	9q31	Medulloblastoma	Multiple basal palmar and plantar pits	Jaw cysts, ovarian fibromas, skeletal abnormalities

Table 5.17 Major familial tumour syndromes involving the nervous system.

the central canal of the spinal cord. They manifest preferentially in children and young adults and usually have an intraventricular or spinal location. Histologically, they are cellular, with typical perivascular rosettes. Spinal ependymomas show a high frequency of mutations in the neurofibromatosis gene *NF2*.

Glioneuronal tumours
This group of brain tumours is less frequent and generally carries a favourable prognosis. Some manifest preferentially in children (desmoplastic infantile astrocytoma/ganglioglioma, dysembryoplastic neuroepithelial tumour), others preferentially in adolescents and adults (gangliocytoma, ganglioglioma, central neuro-

cytoma). They often cause a long-term history of epileptic seizures.

Embryonal tumours
These neoplasms are derived from embryonal or fetal precursor cells, typically manifest in children, and are highly malignant but often respond to radio- or chemotherapy. In the central nervous system, cerebellar medulloblastomas are most common. The peak age at manifestation is 3-6 years; only 20% develop in adults. Occasionally, they occur in the setting of inherited cancer syndromes, including Turcot syndrome (in association with familial polyposis colon cancer) and naevoid basal cell carcinoma syndrome (associated with *PTCH* germline muta-

tions). Neuroblastomas originate from migrating neuroectodermal cells targeted for the adrenal medulla and sympathetic nervous system, which are the principal
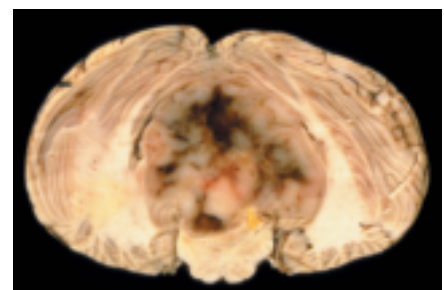

Fig 5.153 Macroscopic image of a medulloblastoma of the cerebellar vermis, compressing the brainstem.
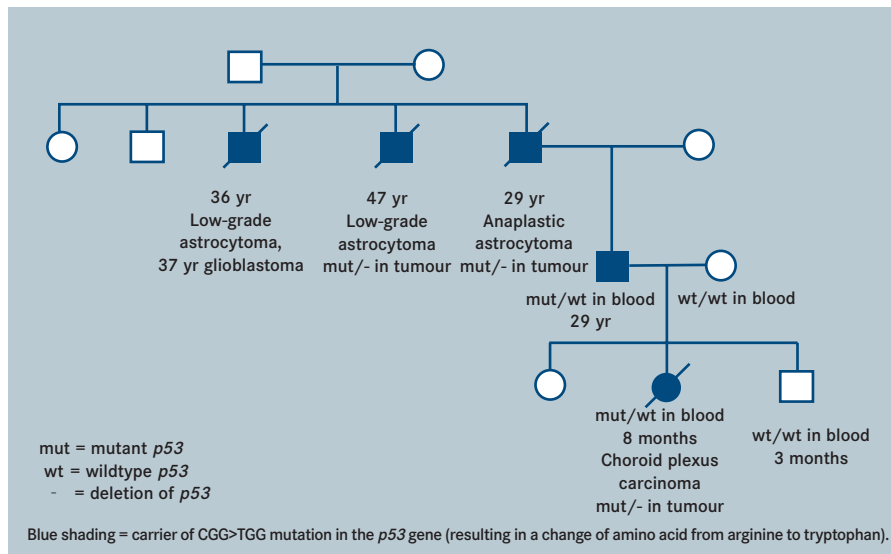
Fig. 5.154 Pedigree of a family with by Li-Fraumeni syndrome, caused by a germline mutation in codon 248 of the *p53* tumour suppressor gene. Blood samples of affected family members have a mutation in one allele. In tumours, the second allele is usually deleted. This family shows a remarkable clustering of brain tumours.

nerve sheath tumours represent typical manifestations of the neurofibromatosis type 1 syndrome.

Meningiomas
These slowly growing, usually benign, neoplasms develop from arachnoidal cells in the meninges. They preferentially affect women, particularly those located in the spine. Meningiomas do not infiltrate the brain but may cause symptoms of intracranial pressure due to compression of adjacent brain structures (WHO Grade I). Preferential sites are the cerebral hemispheres. Meningiomas can often be cured by surgical resection. Malignant meningiomas are much less frequent; they may infiltrate the brain and often recur locally.

Outlook
Although not very frequent, brain tumours contribute significantly to morbidity, often affect children and overall have a poor prognosis. Due to marked resistance to radiation and chemotherapy, the prognosis for patients with glioblastomas is very poor. The majority of patients die within 9–12 months and less than 3% survive more than 3 years. Many genetic alterations involved in the development of nervous tissue tumours have been identified and may lead to novel therapeutic approaches, including gene therapy.

tumour sites. They manifest as an abdominal mass almost exclusively in children less than 10 years old, with a peak incidence of 1-4 years. Tumours in very young children and tumours outside the adrenal medulla have a better prognosis, and some lesions regress spontaneously. Amplification of the *N-MYC* gene indicates a poor prognosis.

Tumours of peripheral nerves
Most of these tumours develop from myelin-producing Schwann cells and are termed neurinomas or schwannomas. Bilateral acoustic schwannomas are diagnostic of the inherited neurofibromatosis type 2. They are benign (WHO Grade I) and rarely recur after surgical resection. Neurofibromas and malignant peripheral

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