Cancer and its management

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6th edition

WILEY-BLACKWELL
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This edition of *Cancer and its management* is dedicated to the memory of
Dr Gabriela Tobias (1950–2008)

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Foreword

Few medical textbooks that are entirely written by two people are alive and well almost 25 years after the first edition. They, and their authors, are usually submerged by changes in the subject and the difficulty and effort required in keeping up to date. This book, however, has the advantage of its primary purpose, which is to provide a balanced, readable, synthesis of the practice of cancer medicine: one that is accessible and of value to students and medical professionals, in all disciplines, who encounter cancer in daily practice but who are not themselves specialists in the field.

It is relatively straightforward to identify new treatments and principles that are in the process of becoming, or have become, part of everyday practice. It is more difficult to be sure of what is becoming redundant as a result of change and which should therefore be reduced in content or excluded. Yet without these judgements the book would grow to become yet another indigestible tome that rests on the shelf and is seldom read.

Jeffrey Tobias and Daniel Hochhauser are among the relatively few oncologists capable of providing, over the entire field, the balance, authority and judgement necessary. To be publishing the sixth edition is a great achievement. In their hands the book will surely continue to prosper and will introduce new readers to the human and technical challenges that are at the heart of the care of patients who have cancer.

Robert L Souhami CBE, FMedSci, MD, FRCP
Emeritus Professor of Medicine
University College London
London 2010

Preface

Professor Robert Souhami and I began work on this book almost 30 years ago, and after a 5-year gestation the first edition appeared in 1986. Naturally we are delighted that it remains so popular. In the past, each time we settled down to start work on the new edition we always felt that this time, surely, the changes would be relatively minor. We were always wrong, and on this occasion, following Bob Souhami's retirement and joined for the first time by my close colleague Professor Daniel Hochhauser, I now discover that the necessary amendments, alterations and updates are greater than ever before.

It was a great pleasure working with Robert for so long, and from my own point of view, our book remains a lasting reminder of an exceptionally close working relationship over so many years. I am delighted that Daniel has agreed to join me in the challenging task of producing this sixth edition of *Cancer and its management*. As on all the previous occasions, we have been astonished by the scale of the innovations and changes in management that have rapidly become an essential part of the gold-standard care of cancer patients. Perhaps it is only by writing a book covering all aspects of malignant disease that these developments can be fully appreciated, though this is not an approach to what is now called continued professional development that we recommend to others!

Bidding a professional farewell to a highly respected close friend and colleague, and warmly welcoming a new one, set me to thinking about some of the changes that have occurred over the past 30 years, though they are far too numerous, of course, to list separately. Without question, the outlook has changed dramatically, and for the better. Patients now have access to a far more integrated and seamless service, with multidisciplinary teams regularly meeting to discuss all aspects of a patient's management, resulting in a more balanced and expert approach to decision-making. Patients are increasingly managed by well-informed specialists with particular experience and expertise in their field of practice. Communication between general practitioners, hospital specialists and community services, including those for continuing and palliative care, have improved enormously.

New chemotherapeutic agents have appeared at a remarkably rapid rate. Most notable of all, even since the last (fifth) edition of this book appeared in 2005, we have seen the increasing and now routine use of biologically targeted therapies in a wide variety of malignant conditions, though it seems hard to believe that these agents, so ubiquitous today, have been available for only a decade or less. The very first of these, the monoclonal antibody rituximab, was approved in the USA by the Food and Drug Administration (FDA) for the treatment of relapsed low-grade CD20-positive non-Hodgkin's lymphoma as recently as the latter part of 1997. This relatively recent discovery has in turn led to the introduction of a huge spectrum of new targeted agents and monoclonal antibodies against the many cellular targets known to be involved in cancer cell growth. An even greater number are in development and we can further predict that microarray diagnostic techniques will lead to far more precise identification of patients who will gain the greatest benefit from the multitude of these newer treatments. It is an exciting time to be in cancer medicine, but it is profoundly important to remember that the human, pastoral and technical lessons of the past do not change. Our book is based largely on these. Virtually all other areas of cancer medicine have seen dramatic improvements as well, whether it be early detection and referral, improved diagnosis, surgical techniques or other major areas of clinical management.

As we pointed out in the preface to previous editions, a textbook limited to this size and designed to be widely comprehensible demands that only essential information be presented. We have had to synthesize and abbreviate a variety of differing, sometimes conflicting, opinions, and summarize interesting or unresolved controversies which, in a larger text, would have been the subject of more detailed discussion. Nonetheless, we hope the result is an accessible text that avoids being too didactic in tone or

synoptic in style. The aim of the book has not altered: it is to provide an introductory text for medical staff, nurses and other allied professionals, students and scientists interested in and challenged by the problems of cancer care.

Initially we wrote this book because we were aware that many busy physicians, surgeons and gynaecologists, who are not themselves cancer specialists, may find it difficult to keep abreast of areas of considerable importance to them. General surgeons, for example, spend a substantial portion of their time dealing with gastrointestinal and abdominal tumours, yet have little working knowledge of the non-surgical treatment of these conditions. Similarly, gynaecological surgeons need to know more about what the radiotherapist (nowadays more frequently termed 'clinical oncologist') and medical oncologist can offer.

In many medical schools, a student's knowledge of the basics and management of malignant disease is acquired from specialists whose main interest may not be related to cancer. Medical students should surely know more about the disease that in many countries is now the largest cause of mortality as well as being regularly recognized by the public at large as the most feared of all diseases. Needless to say, we hope that postgraduate trainees in medicine, surgery and gynaecology will find the book of value, and that it will also be of help to those beginning a career in clinical or medical oncology. Finally, we would like to think that general practitioners, all of whom look after cancer patients and who have such an important role in diagnosis, early referral of patients with suspicious symptoms, shared management, follow-up and terminal care, will find this book helpful. If specialists in cancer medicine feel it is a useful digest of current thought in cancer management, so much the better. However, this book is not intended primarily for them. There are several very large texts that give specialist advice. Although some of these details necessarily appear in our book, we do not regard it as a handbook of chemotherapy or radiotherapy. To some extent it is a personal view of cancer and its management today and, as such, it will differ in some details from the attitudes and approaches of our colleagues.

We have attempted to give a thorough working knowledge of the principles of diagnosis, staging and treatment of tumours and to do so at a level that brings the reader up to date. We have tried to indicate where the subject is growing, where controversies lie, and from which direction future advances might come. In the first nine chapters we have attempted to outline the essential mechanisms of tumour development, cancer treatment and supportive care. In the remaining chapters we have given an account of the principles of management of the major cancers. For each tumour we have provided details of the pathology, mode of spread, clinical presentation, staging and treatment with radiotherapy and chemotherapy. The role of surgery is of course outlined, but details of surgical procedure are beyond the scope of this book. The references which we have included in the text or for further reading have been chosen because they are clear and authoritative reviews, historical landmarks or, perhaps most excitingly, represent the cutting edge of recent research.

For me personally, the gestation, writing and production of this new edition has been a wonderfully challenging task, enormously enhanced by the arrival of my co-author Professor Daniel Hochhauser, a medical oncologist as passionate and committed as his distinguished predecessor. We both hope that this edition of *Cancer and its management* will live up to the high standards that Robert Souhami always imposed, and that it will be of help to those of you struggling like ourselves to offer the highest standards of care for our cancer patients in a rapidly changing clinical world.

This edition is dedicated to the memory of my late wife Dr Gabriela Tobias (1950–2008), an outstanding general medical practitioner and champion of patient welfare, who died from metastatic cancer of the colon during the preparation of the manuscript. Gaby qualified from University College London and University College Hospital in 1973, and devoted virtually the whole of her professional life to the care of patients in the deprived East End of London. Words cannot sufficiently express my profound sense of gratitude to Professor Hochhauser and his team at University College Hospital, London, who supervised her care with such tireless devotion and expertise. The concept of 'patient-centred care', so widely discussed yet so often poorly understood, takes on profound significance from the other side of the consulting-room desk.

Jeffrey Tobias
London 2010

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We acknowledge the assistance of Professor Martyn Caplin, Royal Free Hospital, London, with the chapter on neuroendocrine tumours (Chapter 15).

My personal thanks also go to my long-suffering secretary Jayshree Kara, who dealt with many alterations, reverses and inconsistencies with unfailing good cheer. Any inaccuracies or shortcomings are of course entirely the responsibility of the authors.

Cover image: Fluorescent *in situ* hybridization image of cells recovered from a Her-2-positive breast cancer. Used with permission from Baylor College of Medicine, Lester & Sue Smith Breast Center's Pathology Core, Houston, TX.

Abbreviations

5-FU	5-fluorouracil
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine
6-MP	6-mercaptopurine
6-MPRP	6-mercaptopurine ribose phosphate
6-TG	6-thioguanine
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
AFP	α-fetoprotein
AJCC	American Joint Committee on Cancer
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia; acute myeloblastic leukaemia
AMML	acute myelomonocytic leukaemia
ANL	acute non-lymphocytic leukaemia
APL	acute promyelocytic leukaemia
APUD	amine precursor uptake and decarboxylation
ASCO	American Society for Clinical Oncology
ATRA	all-*trans*-retinoic acid
BCG	bacille Calmette–Guérin
BCNU	bis-chloroethyl nitrosourea
BMI	body mass index
BMT	bone-marrow transplantation
BrdU	bromodeoxyuridine
BTV	biological target volume
CALLA	common acute lymphoblastic leukaemia antigen
CCNU	*cis*-chloroethyl nitrosourea
CEA	carcinoembryonic antigen
CGL	chronic granulocytic leukaemia
CHART	continuous hyperfractionated accelerated radiotherapy
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CLL	chronic lymphocytic leukaemia
CMF	cyclophosphamide, methotrexate and 5-fluorouracil
CMI	cell-mediated immunity
CML	chronic myeloid leukaemia
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
CTV	clinical target volume
DCIS	ductus carcinoma *in situ*
DHFR	dihydrofolate reductase
DIC	disseminated intravascular coagulation
DPD	dihydropyrimidine dehydrogenase
EBV	Epstein–Barr virus
ECOG	Eastern Cooperative Oncology Group
EF	extended field
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EpCAM	epithelial cell adhesion molecule
EPO	erythropoietin
ER	estrogen receptor
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
FAP	familial adenomatous polyposis
FDA	Food and Drug Administration
FdUMP	5-fluoro-2-deoxyuridine monophosphate
FIGO	International Federation of Gynecology and Obstetrics
FISH	fluorescence *in situ* hybridization
FIT	faecal immunochemical test
FOBT	faecal occult blood test
FSH	follicle-stimulating hormone
G6PD	glucose 6-phosphate dehydrogenase
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GH	growth hormone
GIST	gastrointestinal stromal tumour
GM-CSF	granulocyte/macrophage colony-stimulating factor
GSH	glutathione
GTV	gross tumour volume
HAART	highly active antiretroviral therapy
HBI	hemibody irradiation

HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotrophin
HCL	hairy cell leukaemia
HCV	hepatitis C virus
HDI	HER dimerization inhibitor
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HHV	human herpesvirus
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HNPCC	hereditary non-polyposis colon cancer
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone-replacement therapy
HTLV	human T-cell leukaemia/lymphotropic virus
HVA	homovanillic acid
IF	involved field
IGF	insulin-like growth factor
IL	interleukin
IMRT	intensity-modulated radiation therapy
INRG	International Neuroblastoma Risk Group
INSS	International Neuroblastoma Staging System
IPSID	immune proliferative small-intestine disease
IVU	intravenous urography
KGF	keratinocyte growth factor
KSHV	Kaposi's sarcoma herpesvirus
LAK	lymphokine-activated killer (cell)
LDH	lactate dehydrogenase
LET	linear energy transfer
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LOH	loss of heterozygosity
LVEF	left ventricular ejection fraction
M-CSF	macrophage colony-stimulating factor
MDR	multidrug resistance
MDS	myelodysplastic syndrome
MEN	multiple endocrine neoplasia
MGMT	O^6-methylguanine-DNA methyltransferase
MGUS	monoclonal gammopathy of unknown significance
MHC	major histocompatibility complex
MIBG	meta-iodobenzylguanidine
MMP	matrix metalloproteinase
MRC	Medical Research Council
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MTI	malignant teratoma intermediate
mTOR	mammalian target of rapamycin
MTT	malignant teratoma trophoblastic
MTU	malignant teratoma undifferentiated
NCAM	neural-cell adhesion molecule
NCRI	National Cancer Research Institute
NF	neurofibromatosis
NHL	non-Hodgkin's lymphoma
NICE	National Institute for Health and Clinical Excellence
NK	natural killer (cell)
NLCN	North London Cancer Network
NSABP	National Surgical Adjuvant Breast Project
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small-cell lung cancer
NWF	New Working Formulation
PAS	periodic acid–Schiff (stain)
PCI	prophylactic cranial irradiation
PCR	polymerase chain reaction
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PEL	primary effusion lymphoma
PET	positron emission tomography
PKC	protein kinase C
PLAP	placental alkaline phosphatase
PMBL	primary mediastinal B-cell lymphoma
PNET	primitive neuroectodermal tumour
PR	progesterone receptor
PSA	prostate-specific antigen
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
PTV	planning target volume
REAL	revised European–American lymphoma (classification)
RPA	recursive partitioning analysis
RS	Reed–Sternberg (cell)
RSV	Rous sarcoma virus
RTOG	Radiation Therapy Oncology Group
RT-PCR	reverse-transcriptase polymerase chain reaction
SCLC	small-cell lung cancer
SEER	Surveillance, Epidemiology and End Results (program)
SNCC	small non-cleaved cell (lymphoma)
SVCO	superior vena caval obstruction
TBI	total-body irradiation
TCC	transitional cell carcinoma
Tdt	terminal deoxynucleotidyltransferase
TGF	transforming growth factor
TIBC	total iron-binding capacity
TNF	tumour necrosis factor
TNI	total nodal irradiation

TNM	tumour, node, metastasis
TS	thymidylate synthase
TSH	thyroid-stimulating hormone
UICC	*Union Internationale Contre le Cancer*
UV	ultraviolet
VAIN	vaginal intraepithelial neoplasia
VAP	vincristine, doxorubicin and prednisone
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VIN	vulval intraepithelial neoplasia
VIP	vasoactive intestinal polypeptide
VMA	vanillylmandelic acid
WBC	white blood cell count
WHO	World Health Organization

1 The modern management of cancer: an introductory note

Cancer is a vast medical problem. It is now the major cause of mortality, both in the UK and elsewhere in the Western world [1] (Figure 1.1), diagnosed each year in one in every 250 men and one in every 300 women. The incidence rises steeply with age so that, over the age of 60, three in every 100 men develop the disease each year (Figure 1.2a). It is a costly disease to diagnose and investigate, and treatment is time-consuming, labour-intensive and usually requires hospital care. In the Western world the commonest cancers are of the lung, breast, skin, gut and prostate gland [2,3] (Figures 1.2b and 1.3). The lifetime risk of developing a cancer is likely to alter sharply over the next decade because the number of cancer cases has risen by nearly one-third over the past 30 years. An ageing population, successes from screening and earlier diagnosis have all contributed to the rise. Present estimates suggest that the number of cases is still rising at a rate of almost 1.5% per annum. The percentage of the population over the age of 65 will grow from 16% in 2004 to 23% by 2030, further increasing the overall incidence [4].

For many years the main methods of treating cancer were surgery and radiotherapy. Control of the primary tumour is indeed a concern, since this is usually responsible for the patient's symptoms. There may be unpleasant symptoms due to local spread, and failure to control the disease locally means certain death. For many tumours, breast cancer for example, the energies of those treating the disease have been directed towards defining the optimum methods of eradication of the primary tumour. It is perhaps not surprising that these efforts, while improving management, have not greatly improved the prognosis because the most important cause of mortality is metastatic spread. Although prompt and effective treatment of the primary cancer diminishes the likelihood of recurrence, metastases have often developed before diagnosis and treatment have begun. The prognosis is not then altered by treatment of the primary cancer, even though the presenting symptoms may be alleviated. Progress in treatment has been slow but steady. Worldwide, between 1990 and 2001, the mortality rates from all cancers fell by 17% in patients aged 30–69 years, but rose by 0.4% in those aged 70 years or older [1,5]. This may sound impressive at first reading, but the fall was lower than the decline in mortality rates from cardiovascular disease, which decreased by 9% in the 30–69 year age group (men) and by 14% in the 70 year (or older) age group. In the UK there has been a steady fall in mortality from cancer of about 1% a year since the 1990s (Figure 1.4), but with a widening gap in the differing socioeconomic groups. As the authors forcefully state [2]: 'Increases in cancer survival in England and Wales during the 1990s are shown to be significantly associated with a widening deprivation gap in survival.' In the USA, the number of cancer deaths has now fallen over the past 5 years, chiefly due to a decline in deaths from colorectal cancer, itself thought to be largely due to an increase in screening programmes. Interestingly, the fall in mortality has also been paralleled by a reduction in incidence rates in the USA – for men since 1990 and for women since 1991 [6]. Nonetheless, cancer continues as the leading cause of death in the USA, under the age of 85 years [3].

Every medical specialty has its own types of cancer which are the concern of the specialist in that area. Cancer is a diagnosis to which all clinicians are alerted whatever their field and, because malignant disease is common, specialists acquire great expertise in diagnosis, often with the aid of techniques such as bronchoscopy and other forms of endoscopy. Conversely, the management of cancer once the diagnosis has been made, especially the non-surgical management, is not part of the training or interest of many specialists. This has meant that radiotherapists ('clinical oncologists') and medical oncologists are often asked to see patients who have had a laparotomy at which a tumour such as an ovarian cancer or a lymphoma

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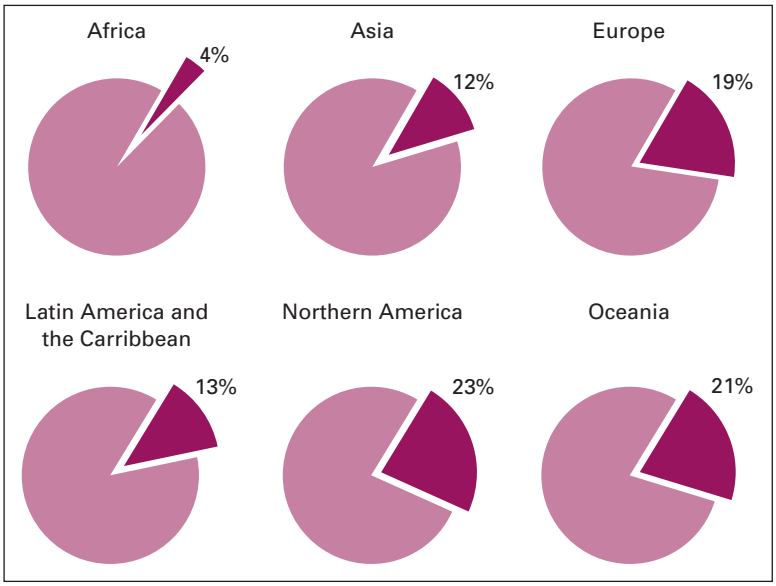
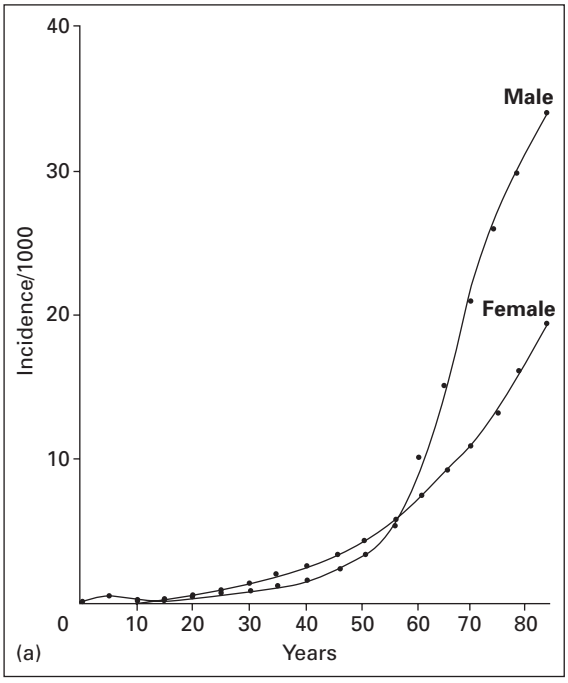


Figure 1.1 Percentage of all deaths due to cancer in the different regions of the world. Available at http://info.cancerresearchuk.org/cancerstats/geographic/world/mortality/?a=5441, accessed 10 September 2008. (© Cancer Research UK.)



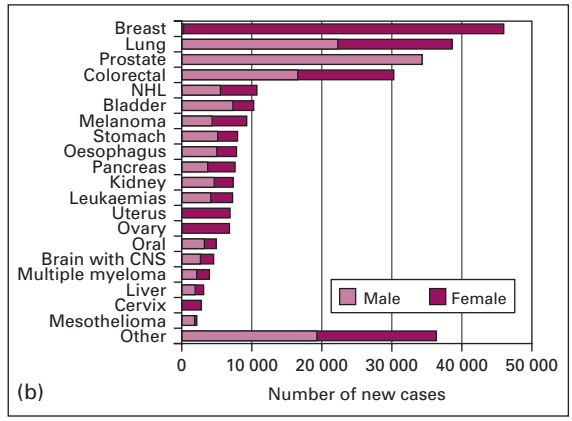
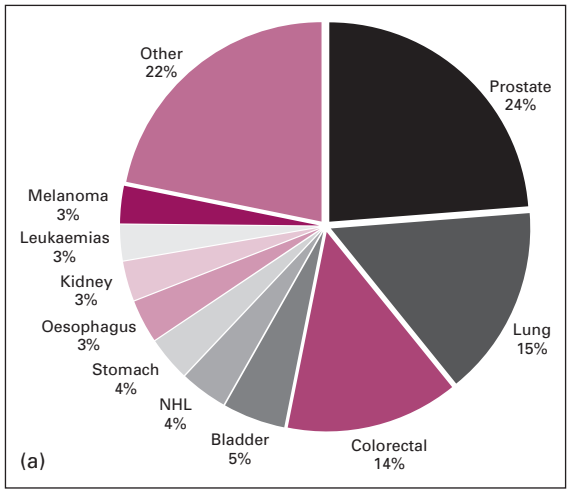


Figure 1.2 (a) Age-specific cancer incidence in England and Wales. (b) The 20 most commonly diagnosed cancers (excluding non-melanoma skin cancer) in the UK, 2005. NHL, non-Hodgkin's lymphoma. Available at http://info.cancerresearchuk.org/cancerstats/incidence/commoncancers/, accessed 10 September 2008. (© Cancer Research UK.)

has been found, but the abdomen then closed without the surgeon having made an attempt to stage the disease properly or, where appropriate, to remove the main mass of tumour. This poses considerable problems for the further management of the patient. More generally, lack of familiarity with the principles of cancer management, and of what treatment can achieve, may lead to inappropriate advice about outcome and a low level of recruitment into clinical trials. An understanding of the principles of investigation and treatment of cancer has become essential for



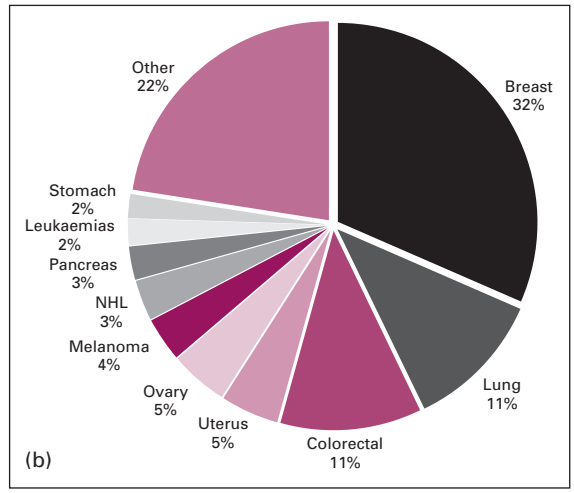


Figure 1.3 (a) The 10 most common cancers in males (excluding non-melanoma skin cancer) in the UK, 2005. Available at http://info.cancerresearchuk.org/cancerstats/incidence/males/, accessed 10 September 2008. (b) The 10 most common cancers in females (excluding non-melanoma skin cancer) in the UK, 2005. Available at http://info.cancerresearchuk.org/cancerstats/incidence/females/?a=5441, accessed 10 September 2008. NHL, non-Hodgkin's lymphoma. (© Cancer Research UK.)

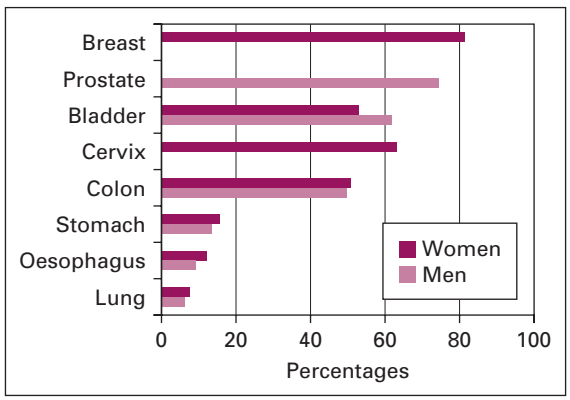


Figure 1.4 Cancer survival rates improved between 1999 and 2004. Available at http://www.statistics.gov.uk/cci/nugget.asp?id=861. (Reproduced under the terms of the Click-Use Licence.)

every physician and surgeon if the best results for their patients are to be achieved.

During the latter part of the last century, advances in the chemotherapy and radiotherapy of uncommon tumours such as Hodgkin's disease and germ-cell tumours of the testis, together with the increasing complexity of treatment decisions in more common tumours, led to a greater awareness of the importance of a planned approach to clinical management. This applies not only for the problems in individual patients, but also in the planning of clinical trials. For each type of cancer, an understanding of which patients can be helped, or even cured, can only come by close attention to the details of disease stage and pathology. Patients in whom these details are unknown are at risk from inappropriate over-treatment or from inadequate treatment, resulting in the chance of cure being missed. Even though chemotherapy has not on the whole been of outstanding benefit to patients with diseases such as squamous lung cancer or adenocarcinoma of the pancreas, it is clearly essential that clinicians with a specialized knowledge of the risks and possible benefits of chemotherapy in these and other diseases are part of the staff of every oncology department. Knowing when not to treat is as important as knowing when to do so.

For many cancers, improvements in chemotherapy have greatly increased the complexity of management. Cancer specialists have a particular responsibility to validate the treatments they give, since the toxicity and dangers of many treatment regimens mean that the clinical indications have to be established precisely. In a few cases an imaginative step forward has dramatically improved results and the need for controlled comparison with previous treatment is scarcely necessary. Examples are the early studies leading to the introduction of combination chemotherapy in the management of advanced Hodgkin's disease, and the

Table 1.1 The 5-year relative survival for adults diagnosed with major cancers during 1998–2001 and 1999–2003, England.

Cancer		1998–2001 survival (%)	1999–2003 survival (%)
Breast	Women	79.9	81.0
Colon	Men	49.4	49.6
	Women	50.2	50.8
Lung	Men	6.3	6.5
	Women	7.5	7.6*
Prostate	Men	70.8	74.4

* It was not possible to produce an age-standardized 5-year survival figure for lung cancer in women; therefore this figure refers to the unstandardized estimate.
Source: Cancer survival increases in England. Available at http://www.statistics.gov.uk/pdfdir/can0807.pdf. (Reproduced under the terms of the Click-Use Licence.)

prevention of central nervous system relapse of leukaemia by prophylactic treatment. However, such clear-cut advances are seldom made (see, for example, Table 1.1, which outlines the modest improvement in survival for four major types of cancer between 1998 and 2003 in England). For the most part, improvements in treatment are made slowly in a piecemeal fashion and prospective trials of treatment must be undertaken in order to validate each step in management. Modest advances are numerically nonetheless important for such common diseases. Only large-scale trials can detect these small differences reliably. Collaboration on a national and international scale has become increasingly important, and the results of these studies have had a major impact on management, for example in operable breast cancer. There is always a tendency in dealing with cancer to want to believe good news and for early, uncontrolled, but promising results to be seized upon and over-interpreted. Although understandable, uncritical enthusiasm for a particular form of treatment is greatly to be deplored, since it leads to a clamour for the treatment and the establishment of patterns of treatment that are improperly validated. There have been many instances where treatments have been used before their place has been clearly established: adjuvant chemotherapy in non-small-cell lung cancer, limb perfusion in sarcomas and melanoma, radical surgical techniques for gastric cancer and adjuvant chemotherapy for bladder cancer are examples. The toxicity of cancer treatments is considerable and can only be justified if it is unequivocally shown that the end-results are worthwhile either by increasing survival or by improving the quality of life.

The increasing complexity of management has brought with it a recognition that in most areas it has become necessary to establish an effective working collaboration between specialists. Joint planning of management in specialized clinics is now widely practised for diseases such as lymphomas and head and neck and gynaecological cancer. Surgeons and gynaecologists are now being trained who specialize in the oncological aspects of their specialty. In this way patients can benefit from a coordinated and planned approach to their individual problems.

Before a patient can be treated, it must be established that he or she has cancer, the tumour pathology must be defined, and the extent of local and systemic disease determined. For each of these goals to be attained the oncologist must rely on colleagues in departments of histopathology, diagnostic imaging, haematology and chemical pathology. Patients are often referred in whom the diagnosis of cancer has not been definitely made pathologically but is based on a very strong clinical suspicion with suggestive pathological evidence, or where a pathological diagnosis of cancer has been made which, on review, proves to be incorrect. It is essential for the oncologist to be in close contact with histopathologists and cytologists so that diagnoses can be reviewed regularly. Many departments of oncology have regular pathology review meetings so that the clinician can learn of the difficulties which pathologists have with diagnosis and vice versa. Similarly, modern imaging techniques have led to a previously unattainable accuracy in preoperative and postoperative staging, although many of these techniques are only as reliable as the individuals using them (e.g. abdominal or pelvic ultrasound). The

cancer specialist must be fully conversant with the uses and limitations of imaging methods. The techniques are expensive and the results must be interpreted in the light of other clinical information. The practice of holding regular meetings to review cases with specialists from the imaging departments has much to commend it.

Modern cancer treatment often carries a substantial risk of toxicity. Complex and difficult treatments are best managed in a specialized unit with skilled personnel. The centralization of high-dependency care allows staff to become particularly aware of the physical and emotional problems of patients undergoing treatments of this kind. Additionally, colleagues from other departments such as haematology, biochemistry and bacteriology can more easily help in the investigation and management of some of the very difficult problems which occur, for example in the immunosuppressed patient.

The increasingly intensive investigative and treatment policies which have been adopted in the last 25 years impose on clinicians the additional responsibility of having to stand back from the treatment of their patients and decide on the aim of treatment at each stage. Radical and aggressive therapy may be essential if the patient is to have a reasonable chance of being cured. However, palliative treatment will be used if the situation is clearly beyond any prospect of cure. It is often difficult to decide when the intention of treatment should move from the radical to the palliative, with avoidance of toxicity as a major priority. For example, while many patients with advanced lymphomas will be cured by intensive combination chemotherapy, there is no prospect of cure in advanced breast cancer by these means, and chemotherapy must in this case be regarded as palliative therapy. In this situation it makes little sense to press treatment to the point of serious toxicity. The judgement of what is tolerable and acceptable is a major task in cancer management. Such judgements can only come from considerable experience of the treatments in question, of the natural history of individual tumours and an understanding of the patient's needs and wishes.

Modern cancer management often involves highly technological and intensive medical care. It is expensive, time-consuming and sometimes dangerous. Patients should seldom be in ignorance of what is wrong with them or what the treatment involves. The increasingly technical nature of cancer management, and the change in public and professional attitudes towards malignant disease, have altered the way in which doctors who are experienced in cancer treatment approach their patients. There has been a decisive swing towards honest and careful discussion with patients about the disease and its treatment. This does not mean that a bald statement should be made to the patient about the diagnosis and its outcome, since doctors must sustain the patient with hope and encouragement through what is obviously a frightening and depressing period. Still less does it imply that the decisions about treatment are in some way left to the patient after the alternatives have been presented. Skilled and experienced oncologists advise and guide patients in their understanding of the disease and the necessary treatment decisions. One of the most difficult and rewarding aspects of the management of malignant disease lies in the judgement of how much information to give each particular patient, at what speed, and how to incorporate the patient's own wishes into a rational treatment plan.

The emotional impact of the diagnosis and treatment can be considerable for both patients and relatives. Above everything else, treating patients with cancer involves an awareness of how patients think and feel. All members of the medical team caring for cancer patients must be prepared to devote time to talking to patients and their families, to answer questions and explain what is happening and what can be achieved. Because many patients will die from their disease, they must learn to cope with the emotional and physical needs of dying patients and the effects of anxiety, grief and bereavement on their families.

In modern cancer units management is by a team of healthcare professionals, each of whom has their own contribution to make. They must work together, participating in management as colleagues commanding mutual respect. The care and support of patients with advanced malignant disease and the control of symptoms such as pain and nausea have greatly improved in the last 10 years. This aspect of cancer management has been improved by the collaboration of many medical workers. Nurses who specialize in the control of symptoms of malignancy are now attached to most cancer units, and social workers skilled in dealing with the problems of malignant disease and bereavement are an essential part of the team. The development of hospices has led to a much greater appreciation of the way in which symptoms might be controlled and to a considerable improvement in the standard of care of the dying in general hospitals. Many cancer departments now have a symptom support team based in the hospital but who are able to undertake the care of patients in their own homes, giving advice on control of symptoms such as pain and nausea and providing support to patients' families.

There have been dramatic advances in cell and molecular biology in the last 20 years, with the result that our

understanding of the nature of malignant transformation has rapidly increased. This trend will continue, placing many additional demands on oncologists to keep abreast of both advances in management and the scientific foundations on which they are based. The power of modern techniques to explore some of the fundamental processes in malignant transformation has meant that cancer is at the heart of many aspects of medical research, and has led to an increased academic interest in malignancy. This, in turn, has led to a more critical approach to many aspects of cancer treatment. Cancer, and its management, is unquestionably among the most complex and demanding disciplines within medicine, and many more healthcare workers now recognize that cancer medicine is a profoundly rewarding challenge. Standards of patient care have improved dramatically as a result of these welcome changes.

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2 Epidemiology, cure, treatment trials and screening

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The epidemiology of cancer, which concerns the study of the frequency of the disease in populations living under different conditions, has been illuminating in many ways. It has allowed the testing of theories about the cause of a cancer by correlating factors related to lifestyle, occupation or exposure to infection with the incidence of a cancer. It has suggested ways in which cancer might be prevented by changing the prevalence of a postulated aetiological agent, as shown by the decline of lung cancer in doctors who have given up smoking. It has provided a stimulus for research into the biological basis of the induction of cancer by these exposures. Finally, epidemiological evidence has proved invaluable in planning cancer services.

Terminology and methods in epidemiology

Prevalence means the proportion of a defined group having a condition at a single point in time. *Incidence* means the proportion of a defined population developing the disease within a stated time period. *Crude incidence* or *prevalence rates* refer to a whole population. *Specific rates* refer to selected groups, for example a higher crude incidence of breast cancer in one population might be due to more postmenopausal women being in the population in question. *Standardized populations* should therefore be used when comparing incidence and prevalence.

In trying to find connections between a disease and a postulated causal factor, epidemiologists may construct either *case–control* or *cohort* studies. For example, to determine if there is a connection between dietary fat and breast cancer, a *case–control study* would compare the dietary intake of people with the disease (cases) and those without (controls). Choosing appropriate controls is vital to the study design. Case–control studies are also suitable for studies of rare tumours in which a group of people who are exposed to the putative aetiological agent are followed and the frequency of the disease is measured. The control group is unexposed, or exposed to a lesser extent. In the case of dietary fat and breast cancer, a *cohort study* would compare the incidence of the disease, over a given period of time, in those with, say, a high-fat and a low-fat diet. If the cancer incidence is low, as it usually is, large numbers of women will be followed over many years before an answer is obtained. Other variables must be allowed for, since eating habits, for example, are influenced by social class and ethnic origin and these may in turn be independently linked to the likelihood of developing breast cancer. Cohort studies take a long time, are very expensive and are unsuitable for studies of rare tumours.

There are considerable problems in the interpretation of data obtained from epidemiological studies. A possible

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relationship between a characteristic and a cancer may be discovered, but there are several considerations that should influence us in deciding whether a causal connection really exists.

1 *Is the relationship between the characteristic and the disease specific, or can a similar association be found with other diseases?* An association with other diseases does not necessarily invalidate a causal connection but may suggest that both the characteristic and the cancer are themselves associated with another factor. For example, both lung cancer and coronary artery disease are more common in social classes 4 and 5. The problem is then to determine if these diseases are due to social class itself or to the higher frequency of cigarette smoking in these social groups.

2 *Is the relationship a strong one?* The likelihood of a causal connection is strengthened if, for example, the risk of cancer in the population showing the characteristic is increased 10-fold rather than doubled.

3 *Is the degree of risk correlated with amount of exposure?* This is the situation with lung cancer and cigarette smoking (Figure 2.1b) and with length of exposure to hormone replacement therapy and breast cancer (Figure 2.1a). Such a gradation greatly increases the likelihood of a causal connection.

4 *Is the association biologically plausible?* For example, it appears intuitively reasonable to accept an association between smoking and lung cancer, but the relationship between smoking and bladder cancer is at first more surprising (see page 334). However, it may be difficult to assess the biological basis for an association since often we do not know the explanation for these events until further investigation, perhaps prompted by the discovery of an association, reveals it. Animal models of the disease may help both in suggesting which environmental agents may be causal and in strengthening the conclusions of epidemiological investigations.

5 *Is there an alternative explanation for what has been found and do the findings fit with other epidemiological data?* The nature of epidemiological evidence is such that absolute proof that an association is causal may sometimes be impossible to obtain except by intervention studies in which the suspected factor is altered or removed to see if the incidence of cancer then falls. Such studies are difficult, expensive and time-consuming, especially if randomization is necessary. In some circumstances randomized intervention may be impossible (we cannot randomly allocate people to give up smoking or to continue!) and the epidemiological data derived from studies of the population provide the only possible information.

Geographical distribution of cancer

Clues to the aetiology of cancer have been obtained from studies of the difference in incidence of cancers in different countries, races and cultures. There are obvious difficulties in obtaining reliable data in some countries. Problems of different age distributions can to some extent be overcome by using age-standardized incidence and by restricting the comparison to the mature adult population aged 35–64 years. This age range excludes the ages where the figures are likely to be least reliable. A further difficulty lies in incomplete documentation of histological type. Sometimes the registration refers to the whole organ – bone or lung – without specifying histological type.

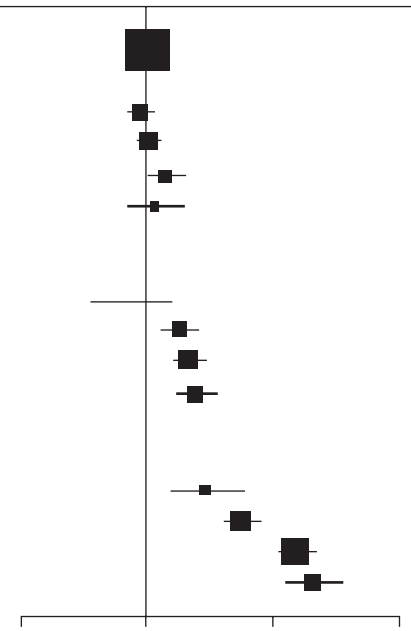
Very large differences in incidence of various tumours between countries have been disclosed (Table 2.1). The very high incidence of liver cancer in Mozambique may be related to aflatoxin mould on stored peanuts, and the incidence is now falling since steps have been taken to store the peanuts under different conditions. In the Ghurjev region of Kazakhstan, carcinoma of the oesophagus is

Table 2.1 Geographical variation in cancer incidence.

Cancer type	Ratio high : low	High incidence	Low incidence
Oesophagus	200 : 1	Kazakhstan	Holland
Skin	200 : 1	Queensland	India
Liver	100 : 1	Mozambique	Birmingham
Nasopharynx	100 : 1	China	Uganda
Lung	40 : 1	Birmingham	Ibadan (Nigeria)
Stomach	30 : 1	Japan	Birmingham
Cervix	20 : 1	Hawaii, Colombia	Israel
Rectum	20 : 1	Denmark	Nigeria

Total duration of use of HRT by type of HRT used at baseline	Cases/population	Relative risk (95% confidence interval)*
Never users of HRT	2894/392 757	1.00 (0.96–1.04)
Past users of HRT		
<1 year	311/47 606	0.94 (0.84–1.05)
1–4 years	384/55 823	1.01 (0.92–1.12)
5–9 years	230/29 614	1.14 (1.00–1.30)
>10 years	80/11 664	1.05 (0.84–1.30)
Current users of estrogen-only HRT		
<1 year	25/4452	0.81 (0.55–1.20)
1–4 years	251/29 582	1.25 (1.10–1.41)
5–9 years	416/47 310	1.32 (1.20–1.46)
>10 years	277/31 862	1.37 (1.22–1.54)
Current users of estrogen–progestogen combinations		
<1 year	97/9771	1.45 (1.19–1.78)
1–4 years	582/49 240	1.74 (1.60–1.88)
5–9 years	850/56 912	2.17 (2.03–2.33)
>10 years	362/23 673	2.31 (2.08–2.56)

(a)



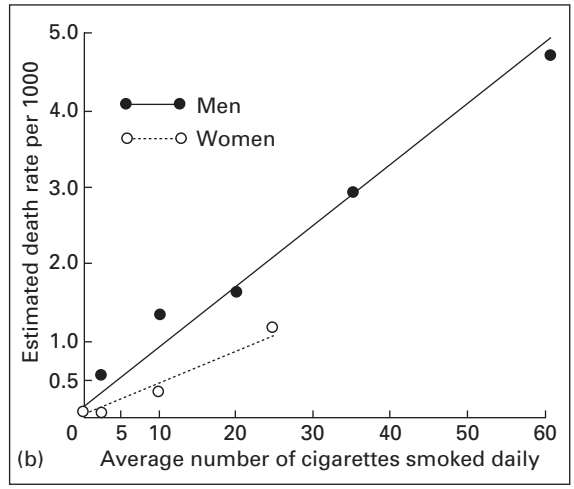


Figure 2.1 (a) Risk of breast cancer related to use of hormone replacement therapy (HRT). (Data from Million Women Study Collaborators [1].) (b) Mortality from cancer of the lung related to number of cigarettes smoked daily. (Data from Doll & Bradford Hill [2].)

200 times more common than in the Netherlands; and in the Transkei region the incidence of the disease appears to have increased greatly in the last 30 years. The high incidence of carcinoma of the stomach in Japan is in contrast to the UK and the USA where the incidence of the disease is falling [3]. Studies such as these provide strong evidence for environmental factors causing cancer, but there may be an interaction with genetic predisposition (see pages 259–260).

An analysis of the relative contributions of the environmental and genetic components can be made by studying cancer incidence in people who have settled in a new country and who have taken on a new way of life. Japanese immigrants in the USA, for example, have a similar incidence

Table 2.2 Cancer incidence (cases per 100 000 per year) in Japanese immigrants compared with country of origin and residents of adopted country.

	Japanese in Japan	USA (mostly Hawaii)	
		Japanese	White
Stomach	130	40	21
Breast	31	122	187
Colon	8.4	37	37
Ovary	5.2	16	27
Prostate	1.5	15	35

of colon cancer to native Americans but five times that of Japanese in Japan [4] (Table 2.2) and it is therefore clear that this difference in rates is not mainly genetic.

Temporal distribution of cancer

The incidence of cancer in a given community may change with time, providing further clues to aetiology. With rare tumours, this may be more dramatically apparent when a disease appears as a cluster in a given place at a given time. An example would be several cases of acute leukaemia occurring in close proximity in a town within a short space of time. Such clustering has indeed been observed in acute leukaemia [5] and has been suggested for Hodgkin's disease. Chance effects make analysis difficult. However, in the case of Burkitt's lymphoma, outbreaks in Uganda have been shown to spread from one part of a district to another in a way that cannot be attributed to chance but which fits well with an infective aetiology that is widespread in the community but produces cancer in only a few children. Stronger evidence of environmental factors comes from the change in cancer incidence with time. However, the interpretation of these changes with time may be made difficult by changes in registration methods, by shifts in diagnostic accuracy and by the long latent period of many cancers. The dramatic rise in lung cancer in the Western world can be attributed confidently to smoking but the fall in stomach cancer is of unknown cause.

Causes of cancer suggested by epidemiological studies

The realization that cancer might largely be preventable has gained more widespread acceptance in recent years.

Table 2.3 Some aetiological factors.

Ionizing irradiation
Atomic bomb and nuclear accidents: acute leukaemia, breast cancer
X-rays (both diagnostic and therapeutic): bone cancer, acute leukaemia, squamous cell carcinoma of skin
Ultraviolet irradiation: basal and squamous cell skin cancer; melanoma
Background irradiation: ?acute leukaemia

Inhaled or ingested carcinogens
Cigarette smoking: cancers of lung, larynx and bladder
Atmospheric pollution with polycyclic hydrocarbons: lung cancer
Asbestos: mesothelioma, bronchial carcinoma
Nickel: cancer of the lung and paranasal sinuses
Chromates: lung cancer
Arsenic: lung and skin cancer
Aluminium: bladder cancer
Aromatic amines: bladder cancer
Benzene: erythroleukaemia
Polyvinylchloride: angiosarcoma of the liver

Viral causes
Papillomavirus: cancers of the cervix and anus
HHV8: Kaposi's sarcoma
HTLV-1: T-cell lymphoma

HHV, human herpesvirus; HTLV, human T-cell leukaemia/lymphoma virus.

It seems probable that at least 50% of cancers could be avoided by lifestyle changes. Many substances present in the environment or in the diet have been shown to be carcinogenic in animals. The epidemiological approach has been used to investigate the link between human cancers and substances which in animals are known to be carcinogens, and to identify unsuspected carcinogens by observations on human populations without reference to previous animal experiments. Some of the factors known, or strongly suspected, to be carcinogenic in humans are shown in Table 2.3.

It has been estimated that more than one in three of the 7 million annual cancer deaths worldwide are caused by nine potentially modifiable risk factors, many of which are listed in Table 2.3. Others include excess body weight and obesity (particularly for carcinomas of the uterus, rectum and colon and postmenopausal breast cancer), together with physical inactivity and inadequate dietary intake of fruit and vegetables. Alcohol use is clearly associated with hepatic and oesophageal cancers, together with those of the oral cavity and oropharynx. However, some of the

important cancers, including prostate, kidney and lymphoma, seem not to be attributable to any of these specific risks (but see also Chapters 18 and 26). Smoking alone is estimated to have caused about 21% of deaths from cancer worldwide, with alcohol use and low fruit and vegetable intake causing another 5% each.

Inhaled carcinogens

Cigarette smoking has been the subject of epidemiological investigation since the early work of Doll and Hill [2] demonstrated the relationship between smoking and lung cancer. All studies have shown a higher mortality for lung cancer in smokers. This mortality has a dose–response relationship with the number of cigarettes smoked and diminishes with time after stopping smoking. This relationship is discussed further in Chapter 12. Cigarette smoking has also been implicated in the development of carcinoma of the bladder, larynx, pancreas and kidney and is considered to be responsible for 35% of all cancer deaths.

Cigarette smoking is the major known cause of cancer. All other causes are quantitatively less important at present. Reversal of this public health hazard will do more to improve cancer mortality than any other single preventive measure.

Atmospheric pollutants such as chimney smoke and exhaust fumes have been widely suspected as a cause of lung cancer. Polycyclic hydrocarbons, such as 3,4-benzpyrene, are present in these fumes and are known to be carcinogenic in humans. The incidence of lung cancer in men in large cities is two or three times greater than in those living in the country. This increase is small compared with the increase in incidence in smokers compared with non-smokers.

Lifestyle and diet

Evidence is accumulating that diet and body weight are important determinants of cancer risk [6]. There is considerable concern about the rising levels of obesity in the UK population. The increase in weight affects all ages and social classes but to different degrees (Figure 2.2) [7].

The nature of the dietary factors in cancer causation, and the mechanisms involved in tumour production, are poorly understood. In countries where there is a high average daily fat intake the age-adjusted death rate of postmenopausal breast cancer and colon cancer is also high. However, those countries where dietary fat intake is high also tend to be the most heavily industrialized. Furthermore, the total caloric intake is higher in these nations, and a similar association exists for levels of dietary protein. Over-nutrition has been shown to increase the incidence of spontaneous tumours in animals. There is strong evidence that obesity is an aetiological factor in cancers of the breast, endometrium and gallbladder. Case–control studies relating dietary fat to cancer incidence have given conflicting results. A recent meta-analysis has attempted to provide an analysis of the risk but the methodological problems and the interpretation of the results present considerable difficulties. Rather than being causally linked to the cancer, it may be that these dietary constituents are associated with other factors that are themselves causal. Other dietary factors that may be associated with the development of cancer are dietary fibre, which may protect against the development of cancer of the large bowel, and vitamin A analogues (retinoids). However, no change in breast cancer risk has been shown in relation to dietary intake of vitamins C, E and A [8]. Two randomized trials of retinoids in patients at high risk of aerodigestive cancer have failed to demonstrate a protective effect of supplementation.

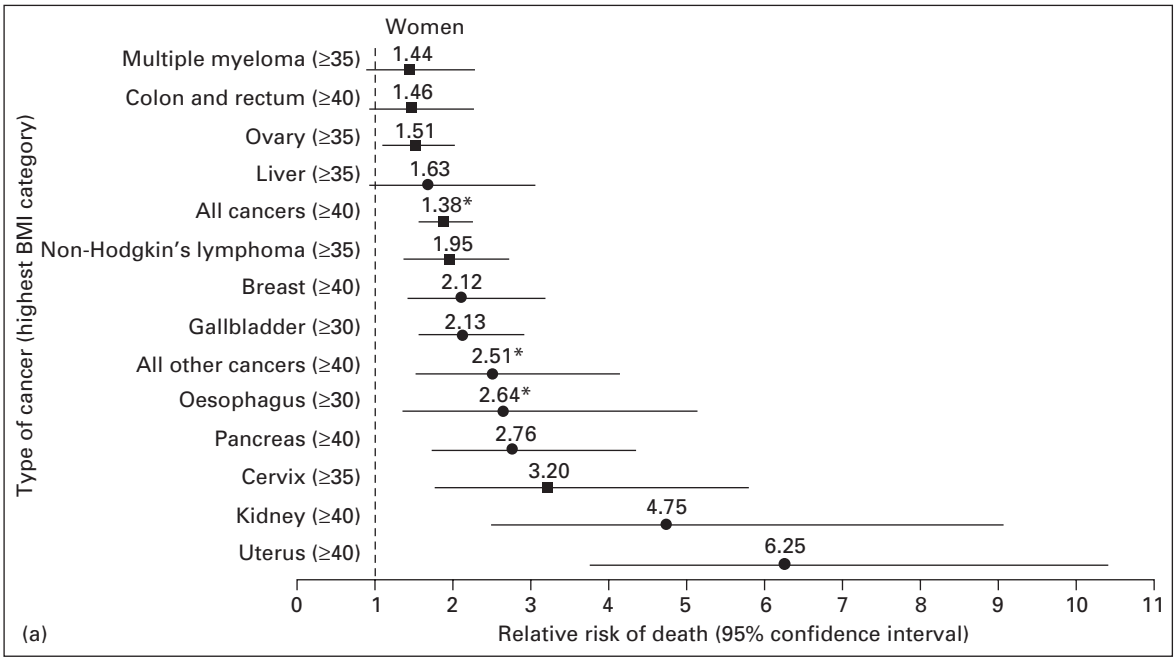
Ionizing irradiation

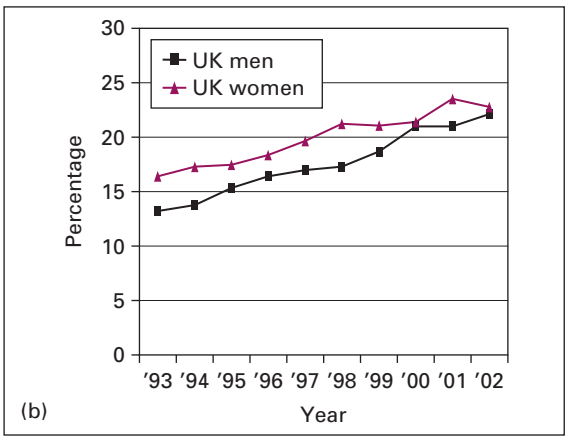
Ionizing irradiation has been well established as a human carcinogen. There has been an increased incidence of leukaemia and breast cancer in the survivors of the Nagasaki and Hiroshima atom bombs. Skin cancer frequently occurred on the hands of radiologists in the days before the significance of radiation exposure was understood. The internal deposition of radium (see Chapter 23, page 411) was a cause of osteosarcoma, as is external beam radiation. There is also an increased incidence of leukaemia in patients treated by irradiation for ankylosing spondylitis. Ultraviolet irradiation is responsible for the increased incidence of skin cancer on sites exposed to intense sunlight. Early intense exposure to sunlight is associated with increased risk of melanoma in later life [9].

Background environmental radiation is at a much smaller dose in total, and is received at a much slower rate ($< 10^{-8}$) compared with diagnostic X-rays. Diagnostic X-rays may account for about 0.6% of cumulative cancer risk [10]. For most cancers, background radioactivity appears to constitute a small risk at present, with the exception of lung cancer, where background radiation from radon is responsible for an increase in incidence [11].

Occupational factors

Aetiological factors in cancer, including occupational factors, are listed in Table 2.3. Asbestos inhalation is associated with two types of cancer: mesothelioma of the pleura and peritoneum, and bronchogenic carcinoma. Prolonged and heavy exposure is needed in the case of bronchogenic cancer, and cigarette smoking further increases the risk. In recent years, the incidence of mesothelioma





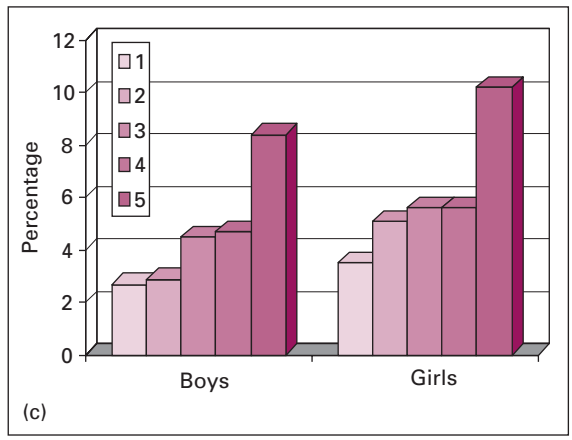


Figure 2.2 Obesity and cancer risk. (a) Relative risk of cancer death in obese vs. normal-weight individuals. BMI, body mass index. (b) Percentage of men and women defined as obese 1993–2002. (c) Obesity in children related to neighbourhood deprivation. Key indicates socioeconomic class. (Data from Sproston & Primatesta [7].)

has risen dramatically in both men and women [12]. This can be related to the widespread use of asbestos in postwar building and the number of cases will continue to rise for the next two decades. There is also an increased risk of lung cancer in workers in nickel refining and the manufacture of chromates, and a possible association with haematite mining and gold mining. Lung cancer has also been described in workers in a sheep-dip factory where there was a very high exposure to inhaled arsenic. These workers had signs of chronic arsenicalism, and the risk of lung cancer with lower levels of exposure is probably very small.

Other human carcinogens have been identified as a result of industrial epidemiological evidence. Aniline dye workers were shown to have a greatly increased incidence of bladder cancer, and this observation led to the