Rachel Airley

Cancer CHEMOTHERAPY

Basic Science to the Clinic

WILEY-BLACKWELL

Cancer Chemotherapy

Rachel Airley

Cancer Research Scientist and Lecturer in Pharmacology

WILEY-BLACKWELL

A John Wiley & Sons, Ltd., Publication

This edition first published 2009
© 2009 by John Wiley & Sons Ltd

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Other Editorial Offices:
9600 Garsington Road, Oxford, OX4 2DQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell

The right of the author to be identified as the author of this work has been asserted in accordance with the Copyright, Designs and Patents Act 1988.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by the UK Copyright, Designs and Patents Act 1988, without the prior permission of the publisher.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book. This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

Library of Congress Cataloguing-in-Publication Data

Airley, Rachel.
Cancer chemotherapy / Rachel Airley.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-470-09254-5 (HB) – ISBN 978-0-470-09255-2 (PB) 1. Cancer–Chemotherapy. I. Title.
[DNLM: 1. Neoplasms–drug therapy. 2. Antineoplastic Agents–therapeutic use. QZ 267 A298c 2009]
RC271.C5A35 2009
616.99'4061–dc22

2008052079

ISBN: 978-0-470-09254-5 (H/B)
ISBN: 978-0-470-09255-2 (P/B)

A catalogue record for this book is available from the British Library.

Set in 10.5/12.5 pt Times by Thomson Digital, Noida, India.
Printed and bound in Great Britain by CPI Antony Rowe, Chippenham, Wiltshire.

First Impression 2009

Cancer Chemotherapy

Preface

While researching this book, I came across a letter in the journal *Nature* asking for caution in the current trend for the use of humorous nomenclature for newly discovered genes[1], the author referring to the tumour suppressor gene *Pokemon*, which I have briefly described in Chapter 4. In this letter, the author reminded us that at a certain point, this name might have to be used by a health professional when discussing a clinical condition with a patient, a sobering thought that served as a reminder that every process started in the laboratory, however prolonged and seemingly removed from the clinic, potentially impacts on the lives of patients. I decided to compile this book after being asked on a number of occasions by pharmacy students at the School of Pharmacy and Chemistry, Liverpool John Moores University if there were a book available that offered a concise, relatively inexpensive and broad introductory text that covered the content of my lecture course in cancer chemotherapy. Specifically, their requests usually came following lectures describing the design, pharmacology and clinical development of novel anticancer agents for which there appeared to be only a limited range of reference sources suitable for undergraduates that didn't involve lengthy searches through the scientific journals. The research and treatment of cancer is a three-way collaboration between health professionals, clinical and experimental scientists, so I have tried to offer a text that unites the topics most pertinent to each group in order to foster a mutual understanding of the role of each at undergraduate level. To this end, the book is aimed at undergraduates of pharmacy, medicine, dentistry, nursing and the allied health professions; as well as providing a useful primer for those considering a career in cancer research, whether they are undertaking a final year dissertation or graduate research project in this area. I have attempted to summarize and consolidate the process behind the research and treatment of cancer, covering topics that range from the clinical aspects of cancer, such as its epidemiology and the role of the many of health professionals involved in its treatment, through to the currently accepted cancer chemotherapy regimens, in particular the classical cytotoxic anticancer agents

[1]Maclean, K. (2006) Humour of gene names lost in translation to patients. *Nature*, **439** (7074), 266.

此为试读,需要完整PDF请访问: www.ertongbook.com

and how they are applied according to cancer diagnosis and staging. I have devoted a large part of the book to the science of cancer research, encompassing basic research into the molecular pathways determining the course of the disease and the methodologies used in target validation, drug discovery and clinical trials. I have also included sections that represent the current state of the art of novel anticancer drug discovery and development. This covers what I would describe as targeted agents, such as the tyrosine kinase inhibitors, some of which have generated excitement and controversy in mainstream newsrooms in recent times. Cancer research is a rapidly evolving field, and although I have made every attempt to provide the most up to date information, it is inevitable that by the time this book comes to publication there will have been further important developments. In order to keep up to date with the progress of novel anticancer agents, I would recommend the web site www.clinicaltrial.gov, and to keep track of newly approved novel agents, the Food and Drug Administration web site provides a search facility www.fda.gov/search/databases.html. Finally, I have included some worked examples of structured essay questions, where I have tried to offer advice that goes beyond the regurgitation of complex chemical structures and offer some insight into exam technique.

It just remains for me to acknowledge the support I have had during this project; at Wylie, my commissioning editor Rachael Ballard and project editor Fiona Woods, who have both showed endless patience through many delays associated with transatlantic moves and working as a real life pharmacist; and the constant support through each new academic challenge of my parents Lorraine and Alan Airley MRPharmS. I would also like to thank the students at Liverpool John Moores University, now also real life pharmacists, who provided me with the original idea for this book.

R.A.
July, 2008

Contents

Preface ix

1 Cancer epidemiology 1
- 1.1 Cancer incidence, prevalence and mortality 1
- 1.2 Childhood cancers 3
- 1.3 Global epidemiology 6

2 Histopathology of cancer 11
- 2.1 Introduction 11
- 2.2 Malignant, benign and normal (non-malignant) tissue 11
- 2.3 Cell death 12

3 Carcinogenesis, malignant transformation and progression 19
- 3.1 Introduction 19
- 3.2 Chemical carcinogenesis 19

4 Molecular biology of cancer: oncogenes and tumour suppressor genes 23
- 4.1 Introduction 23
- 4.2 Oncogenesis 25
- 4.3 Tumour suppressor genes 30

5 Tumour metastasis: a convergence of many theories 37
- 5.1 Introduction 37
- 5.2 Detachment and migration from the primary tumour 37
- 5.3 Intravasation 38
- 5.4 Transport 42
- 5.5 Extravasation 43
- 5.6 Growth of the metastatic tumour mass 45

6 Health professionals in the treatment of cancer **49**
6.1 Introduction 49
6.2 Pathology 49
6.3 Radiology 50
6.4 Role of the surgical oncologist 51
6.5 Oncology pharmacy 52
6.6 Oncology nursing 53
6.7 The NHS Cancer Plan 54

7 Principles of cancer chemotherapy **55**
7.1 Introduction 55
7.2 Timing of chemotherapy 55
7.3 Biomarkers and their uses 59
7.4 Clinical assessment of biomarkers 59
7.5 Pharmacogenetics and pharmacogenomics of cancer chemotherapy 64

8 Classical anticancer agents **67**
8.1 Introduction 67
8.2 Alkylating agents 67
8.3 Antimetabolites 71
8.4 Agents derived from natural or semisynthetic products 77
8.5 Hormonal anticancer agents 106
8.6 Clinically used chemotherapy regimens 111

9 The philosophy of cancer research **117**
9.1 Introduction 117
9.2 Structure of cancer research organizations in the United Kingdom 118
9.3 Cancer research in the United States 120

10 Novel anticancer agents **125**
10.1 Introduction 125
10.2 Target validation 125
10.3 Identification and optimization of lead drugs 146
10.4 Preclinical pharmacology 148

11 Clinical trials **167**
11.1 Introduction 167
11.2 Evaluation of treatment response 169
11.3 Assessment of vascularity and angiogenesis by nuclear medicine technology 173

12 Tumour hypoxia 177
12.1 Introduction 177
12.2 Bioreductive drugs 181
12.3 Inhibitors of HIF-1 and HIF-1-regulated genes 187

13 Antiangiogenic and antivascular agents 199
13.1 History of angiogenesis as a therapeutic target 199
13.2 Anti-angiogenic drug targets 202
13.3 The return of thalidomide 209
13.4 Monoclonal antibodies as anti-angiogenic agents 212
13.5 The hollow fibre assay as a drug screen for anti-angiogenic drugs 213
13.6 Vascular disrupting agents 215

14 Tyrosine kinase inhibitors 217
14.1 Introduction 217
14.2 Tyrosine kinase inhibitors targeting angiogenesis 219
14.3 Non-receptor tyrosine kinase inhibitors 221

15 Ras inhibitors 225

16 Inhibitors of the Akt/PKB pathway 229

17 Targeting stress proteins: HSP90 inhibitors 233

18 The proteasome 237
18.1 Introduction 237
18.2 The proteasome as a target for novel drug strategies 239
18.3 Ubiquitylation as a target 240

19 Checkpoint protein kinases as novel targets – mammalian target of rapamycin (mTOR) 245
19.1 Mammalian target of rapamycin 245
19.2 Structure and activation of mTOR 246
19.3 Novel anticancer agents targeting mTOR 248

20 Telomerase 249

21 Histone deacetylase: an epigenetic drug target 255
21.1 Introduction 255
21.2 HDAC and DNA packaging 255
21.3 HDAC inhibitors 261

22 Pharmaceutical problems in cancer chemotherapy 265
22.1 Manifestation of toxicity 265
22.2 Regimen-related toxicity 269

22.3 Secondary malignancies 270
22.4 Drug resistance 271
22.5 Pharmaceutical complications 274
22.6 Phlebitis and venous irritation 279
22.7 Health and safety 279
22.8 National guidance on the safe administration of intrathecal chemotherapy 279

23 Oncology pharmacy at home and abroad 281

24 Practice exam questions 283

25 Bibliography and further reading 299

Index 331

1

Cancer epidemiology

1.1 Cancer incidence, prevalence and mortality

Every year, more than 285 000 people are diagnosed with cancer in the United Kingdom, and the current estimate is that more than one in three people will develop a form of cancer at some point in their lifetime. There are more than 200 different types of cancer, but four particular tumour types: breast, lung, colorectal and prostate-constitute over half of all new cases diagnosed (Figure 1.1). Cancer incidence, defined as the number of new cases arising in a period of time, is gender and age specific. In males, prostate cancer is the most prolific, where almost 35 000 new cases were diagnosed in 2004, followed by lung cancer, with around 22 000, and bowel cancer, with around 20 000 new cases per year. However, in females, breast cancer continues to be the most common tumour type, the disease accounting for nearly one in three female cancers, with over 44 000 new cases diagnosed in the year 2004. Cancer incidence may be further defined by the lifetime risk of developing the disease. For instance, in females, the risk of developing breast cancer is 1 in 9, and in males, the risk of developing prostate cancer is 1 in 14. In some tumour types, there are considerable gender-related differences in cancer risk; for example, males are nearly twice as likely to develop lung cancer (1 in 13) than women (1 in 23). Cancer occurs mostly in older people, and the risk of developing cancer increases with age. For example, in the 25–34 age group, the rate of diagnosis in males is 1834 cases per 100 000 of the population, and in females, 2782 cases per 100 000. However, in the 75+ age group, the rate of diagnosis in males has risen sharply to 52 831 cases per 100 000 in males and 50 803 cases per 100 000 in females. Overall, in the 10 year period 1995–2004, cancer incidence rate has been relatively constant, with a slight increase of around 1% in males and a slight increase in females of 3%. Broken down by cancer type, the largest increases in incidence rate within this period have been seen in malignant melanoma (43%), uterine (21%), oral (23%) and kidney cancer (14%). Cancer is currently the cause of a quarter of United Kingdom deaths, and around two thirds of all deaths in adults under 65 years. In fact, cancer caused 27% of all deaths in the United Kingdom in 2006; that is 29% in males and 25% in females. Five particular tumour types: lung, colorectal, breast, prostate and oesophagus, are responsible for over half (52%) of all cancer mortality (Figure 1.2). Survival is usually defined as the

Cancer Chemotherapy Rachel Airley
© 2009 John Wiley & Sons, Ltd.

此为试读,需要完整PDF请访问: www.ertongbook.com

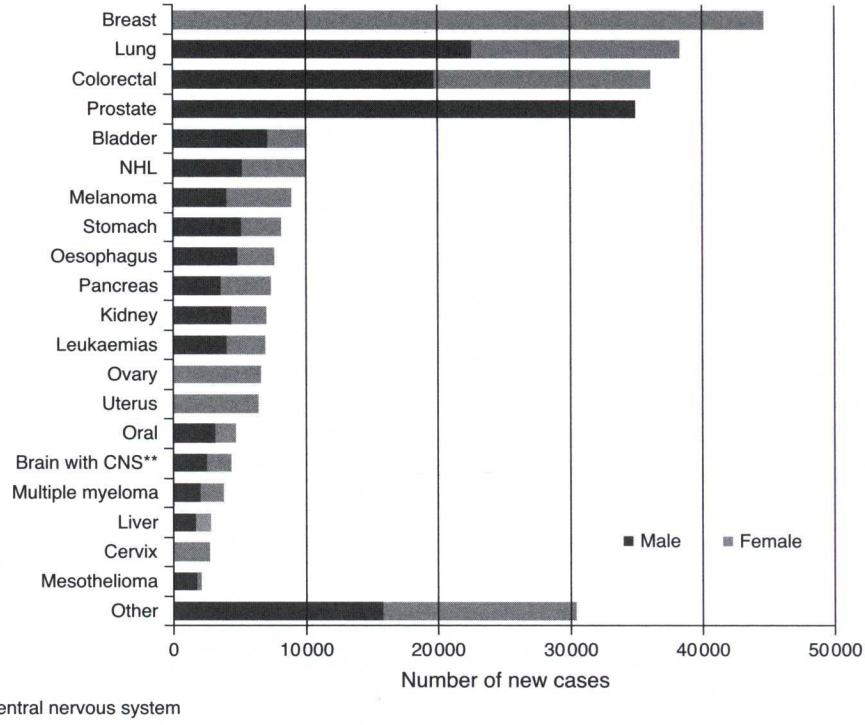

Figure 1.1 The 20 most commonly diagnosed cancers diagnosed in the United Kingdom, 2004. NHL, non-Hodgkin lymphoma. Reproduced with permission from Cancer Research UK http://info.cancerresearchuk.org/cancerstats August 2008.

percentage of patients diagnosed with cancer still alive after a 5 year period. Survival rates vary according to cancer type (Figure 1.3), where cancers may be grouped into three survival bands: 50% or higher, which includes testicular (95%), female breast (77%) and cervix (61%) cancers; 10–50% survival, including colon (47% in males, 48% in females), renal (45% in males, 48% in females) and brain (12% in males, 15% in females); and cancers where less than 10% of all patients are alive after 5 years, notably oesophageal cancer (7% in men, 8% in women), lung (6% in men, 6% in women) and pancreatic (2% in men, 2% in women) cancers. In general, women have higher survival rates than men (43% in men compared to 56% in women), and among adults, survival decreases with increasing age (Table 1.1). This may be due, in part, to mortality that is non-specific to the disease. However, other factors may be contributory, such as the smaller proportion of elderly patients entered into phase I clinical trials. Exceptions to this trend usually occur where the age of the patient at diagnosis is a reflection of the molecular and pathological characteristics of the tumour, for example, breast tumours in premenopausal women tend to be more aggressive, therefore survival rates in these age groups are decreased relative to postmenopausal women.

Progress in the early diagnosis and treatment of cancer has positively affected cancer survival rates. In the United Kingdom, female breast cancer mortality rate has fallen

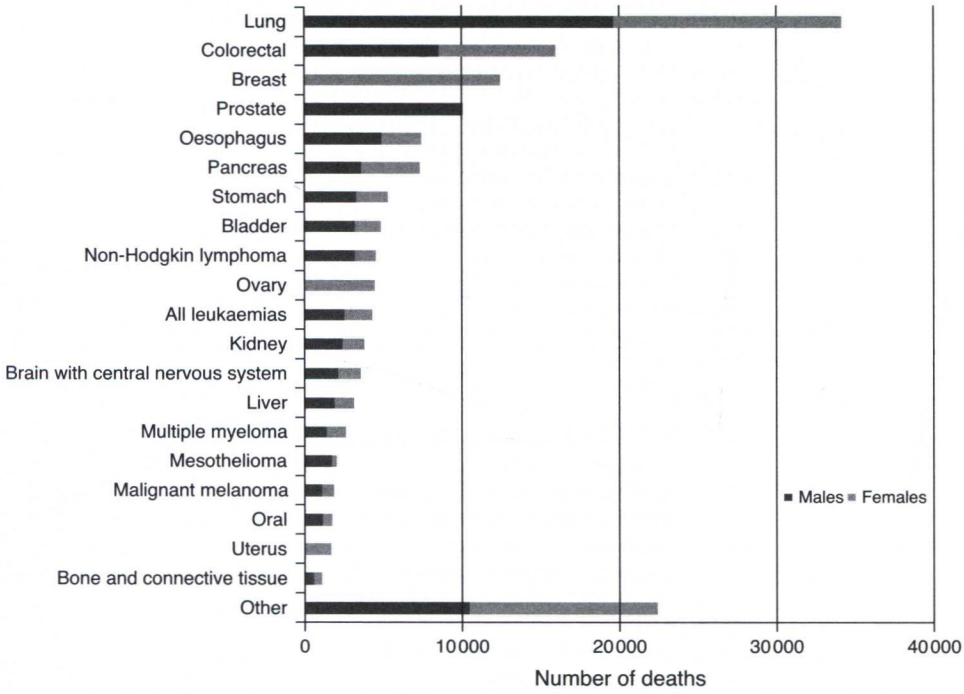

Figure 1.2 The 20 most common causes of death from cancer, persons, United Kingdom, 2006. Reproduced with permission from Cancer Research UK http://info.cancerresearchuk.org/cancerstats August 2008.

sharply, from 15 625 deaths from the disease in 1989 compared with 12 319 deaths in 2006. It is estimated that the National Health Service mammography breast screening programme saves around 1400 lives annually, detecting around 14 000 new cases of breast cancer per year. In prostate cancer, where tests for the biomarker prostate-specific antigen (PSA) have increased the proportion of PSA-detected asymptomatic prostate tumours diagnosed, and because these have an inherently good prognosis, the recorded survival rate has also increased dramatically. This is reflected by the change in 5-year survival rates over the period 1986–1999 (Figure 1.4), where the survival rate for breast cancer increased by an average of 5.4%, and for prostate cancer, by an average of 11.4% every 5 years.

1.2 Childhood cancers

By the age of 15 years, 1 in 500 children will be affected by childhood cancer, which in the United Kingdom means that around 1500 children are diagnosed with cancer every year. Childhood cancer is still relatively infrequent – the most common form being acute lymphoblastic leukaemia, though some rarer cancers are of embryological origin, such as retinoblastoma, rhabdomyosarcoma and neuroblastoma. Together, these were

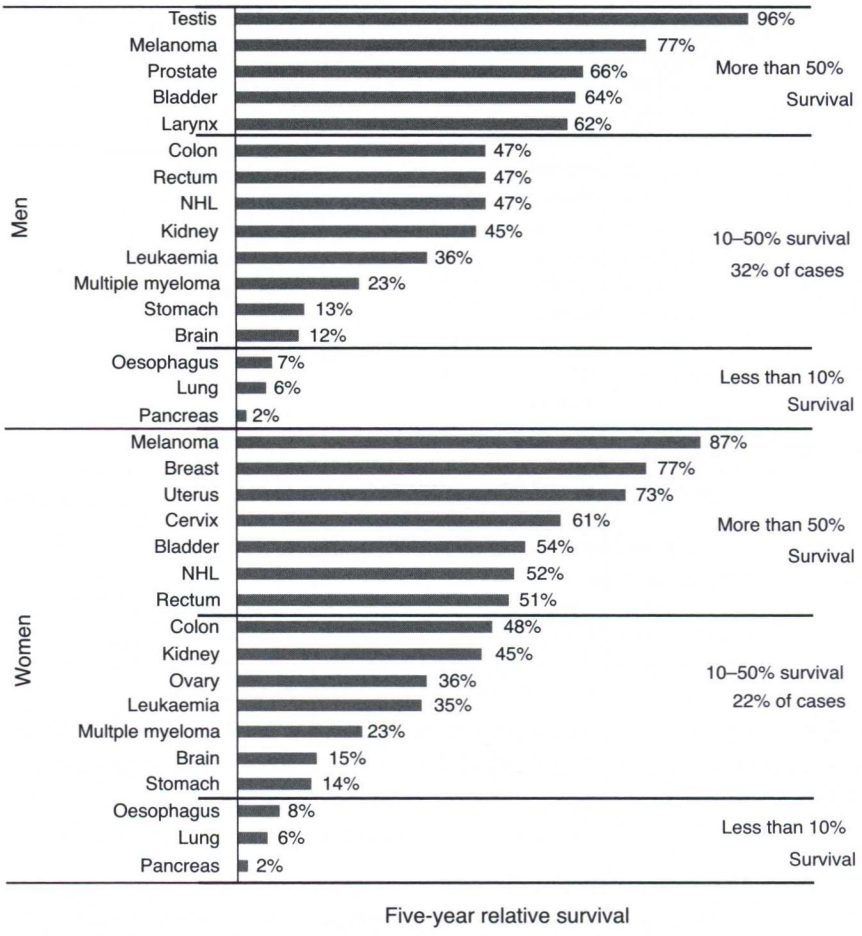

Figure 1.3 Five-year age-standardized relative survival (%) adults diagnosed 1996–1999, England and Wales by sex and site. NHL, non-Hodgkin's lymphoma. Reproduced with permission from Cancer Research UK http://info.cancerresearchuk.org/cancerstats August 2008.

responsible for 1.8% of deaths in children under 15 in the United Kingdom in the time period 2000–2002 (Table 1.2), with an average total of 301 deaths per year (Table 1.3). Figure 1.5 shows mortality rate broken down by cancer type in Great Britain in the time period 1997–2001, where 32% of deaths were caused by leukaemias compared to 1% by retinoblastoma. In all cancer types, survival rates have risen dramatically, where between 1962 and 2001 death rates decreased by an average of 2.6% per year, amounting to a fall of more than half. There has been a steady increase in survival rates in all childhood cancer types, where almost 72% of the cases diagnosed in the time period 1992–1996 have survived for longer than 5 years. This is attributable to the continual refinement and validation of combination chemotherapy regimens made possible by the steady enrolment of children into phase III clinical trials, as well as improved diagnostic techniques. The best example of the sort of improvements in survival rates

Table 1.1 Five-year survival by site and age at diagnosis for patients diagnosed in England and Wales 1996–1999, follow up to 2001

Cancer type	Sex	Age at diagnosis (%)					
		15–39	40–49	50–59	60–69	70–79	80–99
Bladder	Men	90	84	77	70	62	48
	Women	78	70	75	65	53	40
Breast	Women	76	82	85	82	74	58
Cervix	Women	83	73	60	48	36	22
Colon	Men	61	54	50	50	47	40
	Women	58	54	54	52	48	39
Lung	Men	21	9	9	7	5	2
	Women	28	13	11	8	4	1
Ovary	Women	81	55	44	32	23	15
Prostate	Men	76	58	75	77	68	48
Rectum	Men	54	55	54	52	47	34
	Women	60	61	62	58	49	36
Stomach	Men	18	17	15	16	12	7
	Women	19	22	20	19	14	8
Testis	Men	97	96	95	86	67	55
Uterus	Women	77	81	85	78	67	45

Adapted from Cancer Research UK statistics available at http://info.cancerresearchuk.org/cancerstats/survival/age/?a=5441. Accessed 9 October 2008.

Table 1.2 Main causes of child mortality, ages 1–14, by sex and age group, in England and Wales 2000–2002

	Percentages			
	Males		Females	
	1–4 years	5–14 years	1–4 years	5–14 years
Infections	11	3	7	5
Cancers	14	23	13	24
Nervous system and sense organs	14	15	12	14
Circulatory system	4	5	7	6
Respiratory system	9	5	8	8
Congenital anomalies	14	7	15	9
Accident	17	30	16	19
Other	17	12	20	16
All deaths (= 100%) (numbers)	968	1444	752	1049

Taken from Cancer Research UK statistics available at http://info.cancerresearchuk.org/cancerstats/childhoodcancer/mortality/?a=5441. Accessed 9 October 2008.

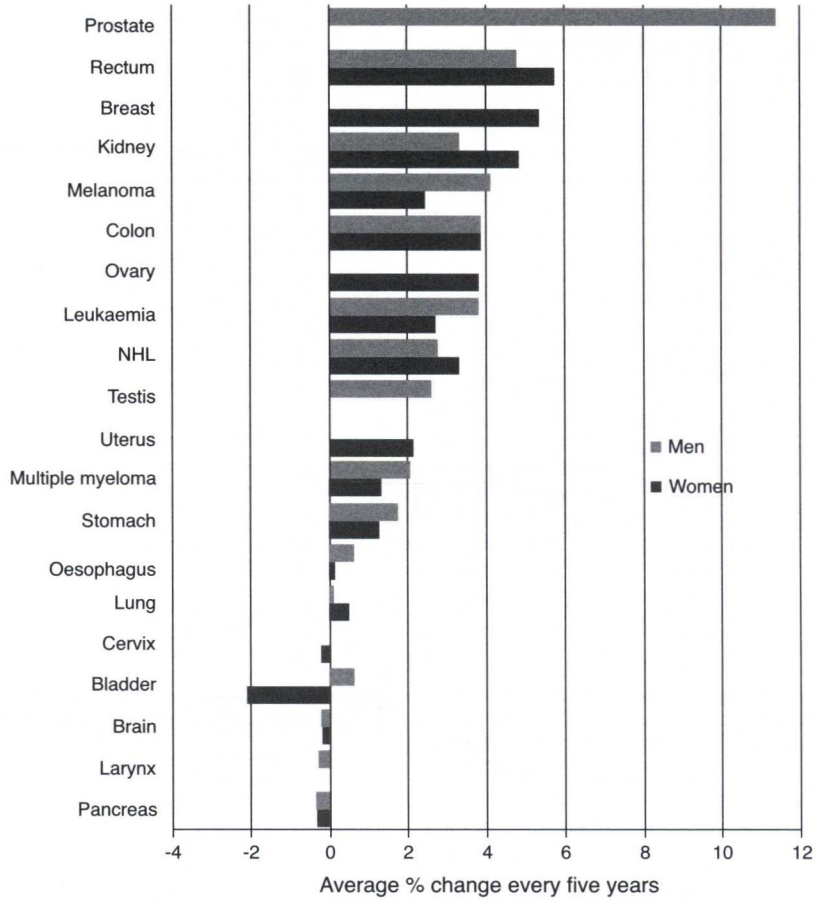

Figure 1.4 Average change (%) every 5 years in 5-year relative survival, by site and sex, adults diagnosed in England and Wales in time period 1986–1999. NHL, non-Hodgkin lymphomas. Reproduced with permission from Cancer Research UK http://info.cancerresearchuk.org/cancerstats August 2008.

achieved is in acute lymphoblastic leukaemia (shown in Figure 1.6 alongside other cancer types), where 5 year survival rate has risen from 12% of cases diagnosed in the time period 1962–1971 to 80% of those diagnosed in the time period 1992–1996.

1.3 Global epidemiology

Global cancer incidence rate (per 100 000 population) for all cancers, as compared with the number of cancer deaths is shown in Figure 1.7, where crude rate is calculated by dividing the number of new cancers diagnosed during a given time period by the number of people in the population at risk. The number of cancer deaths is highest in the United States, which is partially due to large population. However, from the crude incidence rates, it is easily apparent that the population of China, which is significantly

Table 1.3 Annual average number of deaths from cancer before age 15, United Kingdom, 2000–2002 (average rounded to nearest whole number)

Country	Males	Females	Total
England and Wales	148	119	267
Scotland	16	9	25
N Ireland	8	2	9
UK	172	129	301

Taken from Cancer Research UK statistics available at http://info.cancerresearchuk.org/cancerstats/childhoodcancer/mortality/?a=5441. Accessed 9 October 2008.

larger than that of the United States, is considerably less affected by cancer, particularly in women. Incidence rates are broken down by gender, cancer type (lung, bladder, leukaemia, melanoma) and country (United Kingdom, United States, Australia, China, France, Germany and the Netherlands) in Figures 1.8–1.11. These may be explained by differences in lifestyle factors. These include diet, where the chemopreventive properties of soy beans in the Chinese diet, particularly with reference to bladder cancer, have been documented and are reflected in Figure 1.9; and the environment, where there is a notably higher rate of melanoma incidence in Australia due to the risks of sun exposure (Figure 1.11).

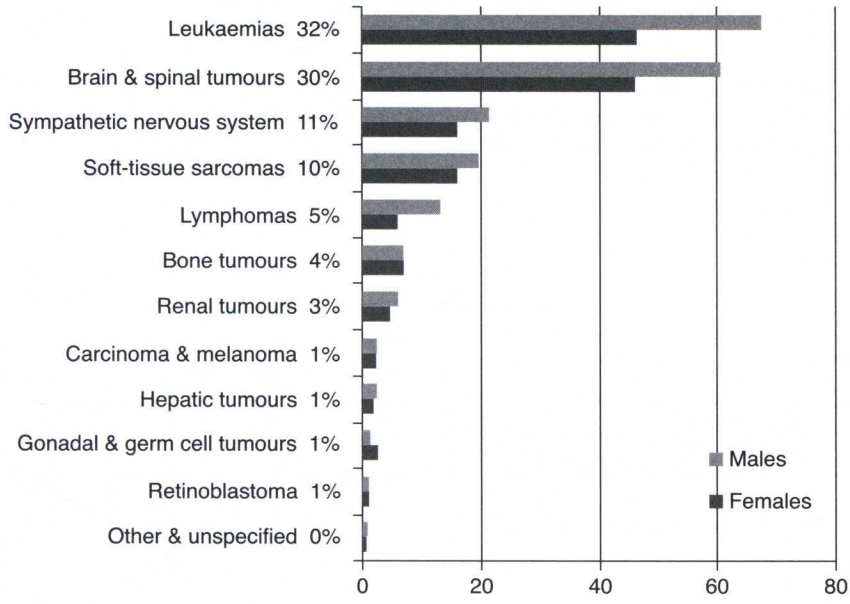

Figure 1.5 Annual average number of deaths in children aged under 15 years previously diagnosed with cancer, by diagnostic group and sex, Great Britain 1997–2001. Reproduced with permission from Cancer Research UK http://info.cancerresearchuk.org/cancerstats August 2008.

此为试读,需要完整PDF请访问: www.ertongbook.com